Exhibit F

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
AT CHARLESTON

IN RE: ETHICON INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION — MDL NO. 2327

THIS DOCUMENT RELATES TO:

WAVE 1 Gynemesh PS CASES

DEFENDANT ETHICON'S EXPERT REPORT OF TIMOTHY A. ULATOWSKI, M.S.

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I. Qualifications

I am an expert consultant on matters concerning medical device regulations, policies, and procedures administered by the Food and Drug Administration (FDA) and related industry standards and best practices. I operate a registered business in the State of Virginia and the County of Fairfax, Virginia under the name Ulatowski Consulting, LLC.

I was awarded a Bachelor of Science degree in 1974 with a major in Microbiology from the Pennsylvania State University. In 1987 I was awarded a Master of Science degree in Physiology/Emphasis in Biomedical Engineering from Georgetown University, School of Medicine, in a collaborative program with Catholic University, Department of Engineering. I have additional college credits in computer science from the University of Maryland and Charles County Community College.

I was an employee of the Food and Drug Administration (FDA) from November 1974 until January 2011. During my 36 plus years of employment with FDA I held increasingly responsible positions, first for 7 years in what is now known as the Center for Drug Evaluation and Research (CDER), and the remaining years in the Center for Devices and Radiological Health (CDRH). CDRH is responsible for evaluating submissions for new medical devices, evaluating medical device clinical investigations, ensuring compliance with medical device laws and regulations administered by the FDA, conducting postmarket vigilance of marketed devices, and conducting research on medical devices.

From 1974 until 1978 I held the position of Microbiologist in the National Center for Antibiotic Analysis in CDER where I conducted laboratory analyses on antibiotics for regulatory certification purposes. From 1978 until 1980 I held the position of Consumer Safety Officer (CSO) in the Office of New Drug Evaluation (ONDE) in CDER. While at ONDE I was a product manager for the Anti-inflammatory Drugs Group and I also contributed to the Oncology and Radiopharmaceutical Drugs Groups. I was the Executive Secretary for the Arthritis Advisory Committee and managed the flow of work and outputs concerning investigational new drug applications (INDs) and New Drug Applications (NDAs). I also was the division lead on major issues such as the Drug Efficacy Study Implementation (DESI) program and the Radiopharmaceutical Drug Research Committee program. In this capacity I became thoroughly familiar with drug regulations, policies, and procedures as well as the related industry standards and best practices.

In 1980 I joined the Office of New Device Evaluation (NDE), Program Management Group, in the Bureau of Medical Devices (BMD) as a CSO. BMD was soon reorganized and joined with the Bureau of Radiological Health to form CDRH. NDE was renamed the Office of Device Evaluation (ODE).

In my first position in CDRH I was assigned to the Investigational Device Staff and was responsible for formulating policies and procedures to implement the new Investigational Device Exemptions regulation, 21 CFR Part 812, and other new human subject protection regulations dealing with informed consent and institutional review boards, 21 CFR Parts 50 and 56. I evaluated Investigational Device

Exemption applications (IDEs) including protocols for clinical studies. I also evaluated and quality controlled the IDE review work of all the divisions in ODE.

In 1988 I was promoted to the Director, IDE Staff. In that capacity I was responsible for managing and directing the IDE staff, for making final decisions on the sufficiency of IDE applications and the review of those submissions by FDA staff, and for IDE regulatory compliance in collaboration with the Office of Compliance, CDRH. In this position I was the CDRH expert on the IDE regulation, policies and procedures. I also became familiar with the industry standards and best practices related to the conduct of clinical studies on medical devices.

Later in 1988 I transferred to the position of Branch Chief, General Hospital Devices in ODE. As Branch Chief I managed and directed the branch staff, and was a primary reviewer of numerous IDE applications, Premarket Notification Submissions (510(k)s), Premarket Approval Applications, new product labeling, medical device reports (MDRs) and other types of regulatory submissions under the purview of my branch. The General Hospital Devices branch evaluated products classified by FDA under 21 CFR Part 880, General Hospital Devices. The products in this classification regulation include, for example, infusion pumps and ports, administration sets and intravascular catheters. When I assumed this position until the end of my FDA career the government classified me as a Supervisory Biomedical Engineer. In this position I was a subject matter expert in premarket submission and medical device reporting regulations, policies and procedures and knowledgeable about industry standards and best practices related to bringing a new device to the market.

In 1991 I was promoted to the position of Associate Director for General Devices in ODE. The scope of my responsibilities expanded to include the premarket evaluation of surgical devices classified under 21 CFR Part 878 as well as the previously assigned general hospital products. In this capacity I had broader influence on guidance, policy and procedure development spanning the entire ODE. I formulated guidance, policies, and was directly involved in the review of many significant new products such as medical lasers and computerized medical systems. As an Associate Division Director, and earlier as a Branch Chief, I instructed ODE reviewers on the policies and procedures regarding premarket submissions. My training to staff included, for example, how to identify and assess predicates and reference device information contained in a 510(k), how to assess technological characteristics and performance data.

In 1996 I was promoted to the Director, Division of Dental, Infection Control and General Hospital Devices in ODE. In this position I assumed responsibility for more product areas and all the premarket regulatory activities associated with those product areas. For example, during the course of my tenure as an ODE division director, I assumed responsibility for anesthesiology devices. During my tenure with FDA I reviewed and made agency decisions on thousands of 510(k)s and dozens of PMAs.

During my tenure at FDA I also participated as a member on FDA committees, national and international standards committees, and the

Global Harmonization Task Force (GHTF).[1] The GHTF created guidance concerning industry standards and best practices related to the life cycle of medical devices and in vitro diagnostics. I was Co-Chair of the FDA committee that created the existing standards program in CDRH. The CDRH standards program evaluates national and international standards to determine if FDA should recognize and utilize them as means to support product development and premarket submissions. During my tenure I also wrote the first FDA guidance documents on infusion pumps and accessories, infusion ports, sterilizers, chemical germicides, and guidance on labeling of devices intended for reuse. I was a member of several Association for the Advancement of Medical Instrumentation (AAMI) and International Standards Organization (ISO) sterilization standards committees.

In 2003 I was promoted to Director, Office of Compliance, CDRH. As the Office of Compliance Director I supervised a large staff that was responsible for ensuring industry and human subject research compliance with the medical device, radiological health, and human subject protection laws and regulations administered by FDA. I had many duties including, for example, directing inspections of medical device manufacturing facilities and clinical research facilities, evaluating Quality System and MDR-related inspection reports and taking regulatory action based on those reports, classifying recall actions, creating risk management strategies, evaluating advertising, labeling and promotional literature, leading the FDA Device Field Committee,[2] and directing responses to violations of import/export and registration laws and rules. In this position I was a subject matter expert in FDA law and regulations concerning medical devices and knowledgeable about related industry standards and best practices.

I transitioned to the position of Senior Advisor for Enforcement in October 2010 in anticipation of my retirement and to allow an orderly succession of leadership. During the last four months of my FDA career I led a team formulating strategies in advance of Congressional user fee reauthorization deliberations and I provided expert advice to senior FDA leadership on premarket and compliance programs. The Commissioner awarded me for my work on user fee legislation.

During my employment with FDA I received virtually every type of award FDA can bestow including the Distinguished Career Service Award, Award of Merit, Commendable Service Awards, and numerous other individual and group awards. I maintained my management and regulatory expertise during the course of my career by attending numerous professional meetings, courses and seminars. I was frequently an invited speaker or major participant at regulatory and professional conferences here and abroad such as those held by the Food and Drug Law Institute, Regulatory Affairs Professional Society, Pharmaceutical Research and Manufacturers of America, and the American Society for Quality. In 2008 Medical Device and Diagnostic Industry News named me to their "100 Notable People" in the medical device industry. I continue to remain current on FDA device regulations, policies and procedures and on related industry standards and best practices.

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[1] The Global Harmonization Task Force has transitioned to the International Medical Device Regulators Forum, www.imdrf.org.

[2] The Device Field Committee members include chief inspectors, senior compliance managers, and other senior FDA officers.

I am currently an independent consultant. I provide consulting services to clients on premarket submissions, postmarket surveillance, labeling, promotion and advertising, and quality systems. I advise medical device and drug manufacturers on compliance matters. I provide litigation testimony on FDA regulations, policies and procedures and industry standards and best practices. I continue to be an invited speaker at professional and industry meetings. Under the auspices of the Department of Commerce and the USAID, I trained international regulators on global medical device premarket and postmarket regulatory policies and procedures and on related industry standards and best practices in October and November 2013 and again in March and May of 2014.

A copy of my curriculum vitae is attached as Appendix A.

NDA Partners LLC bills for my time on this litigation at a rate of $500/hr.

The list of materials that I considered in forming my opinions is attached as Appendix B. I did not rely on any commercial confidential or trade secret information obtained during the course of my employment with FDA in forming my opinions.

II. FDA's Mission, Device Statutory and Regulatory Provisions, and Industry Standards and Best Practices Relevant to the Subject Litigation

II.A. Overview

FDA is a consumer protection agency that has roots stretching back to the turn of the last century. Its statutory authority is derived from the Federal Food, Drug, and Cosmetic Act (the act) (21 USC 301 et seq.)[3] and other acts that have been amended from time to time. Regulations implementing the statutory provisions are published in Title 21, Code of Federal Regulations (21 CFR). The first medical device amendments to the act were enacted on May 28, 1976 and there have been additional amendments in the intervening years.[4]

FDA regulates medical devices. GYNEMESH PS is a medical device. A medical device is defined under 21 USC §321(h) as:

> *"an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is (1) recognized in the National Formulary, or the United States Pharmacopeia, or any supplement to them, (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease in man or other animals, or (3) intended to affect the structure or function of the body in man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent*

[3] References to the act are stated according to United States Code.
[4] Amendments to the act, http://www.fda.gov/regulatoryinformation/legislation/federalfooddrugandcosmeticactfdcact/significantamendmentstothefdcact/default.htm.

upon being metabolized for the achievement of its primary intended purposes."

FDA regulates the entire life cycle of medical devices. For example, FDA evaluates investigational studies for new products before the studies commence,[5] it inspects manufacturing facilities,[6] it evaluates marketing applications, and it monitors the safety and effectiveness of devices during the entire course of their use. FDA regulations govern each of these activities and FDA makes available related guidance documents to inform industry, FDA staff and the public of means to address regulatory requirements.

Industry standards and best practices supplement FDA law and regulations to assist manufacturers throughout the life cycle of a medical device. These standards and best practices are applied by manufacturers in bringing devices to the market, in manufacturing devices, and in postmarket monitoring devices in the marketplace.

II.B. FDA's Medical Device Program

CDRH is the primary organization within FDA that regulates medical devices. Other FDA Centers also have authority to regulate medical devices, primarily those that are a constituent of a combination product. Combination products are therapeutic or diagnostic products that consist of more than one regulated article, e.g., drug/device, and biological/device. Each combination product is regulated by the Center given primary jurisdiction for the specific combination product.

CDRH has over 1000 employees and is organized into offices. For example, ODE is responsible for review of new devices, except for in-vitro diagnostics and radiologic products, the Office of Compliance (OC) is responsible for compliance and enforcement activities and the Office of Surveillance and Biometrics (OSB) is primarily responsible for evaluating medical device reports (MDRs), conducting epidemiology activities, and statistical reviews.

Information from each office within CDRH is integrated by computer systems available for all FDA employees to access and use in the course of performing their jobs. For example, a compliance officer in OC can easily access MDRs, inspection records, and premarket records for specific companies and devices.

CDRH leverages resources from within and outside FDA to accomplish its mission. CDRH leverages the resources of the Office of the Associate Commissioner for Regulatory Affairs, the organizational home of FDA's inspectors, to conduct device manufacturer and clinical investigator inspections. CDRH uses non-FDA, so-called "special government employees", in the fields of medicine, engineering and statistics, and third parties to assist in premarket and compliance activities.

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[5] FDA does not approve "non-significant risk" devices before studies commence. This evaluation and approval is delegated to institutional review boards (21 CFR Part 56).

[6] FDA has authority to inspect all facilities subject to inspection, e.g., all places related to quality system and medical device reporting activities (21 U.S.C. §374).

CDRH obtains information on medical devices for review and analysis by many means. For example, it receives required submissions according to regulations, it proactively collects information and evidence during inspections, it uses public sources of information, and increasingly it relies on regulatory bodies in other countries to provide information on imported FDA-regulated products. FDA has extensive test facilities and conducts laboratory and engineering analyses on regulated products for compliance, premarket, and postmarket surveillance purposes.

II.C. Prohibited Acts, Misbranding and Adulteration and FDA Enforcement of Laws and Regulations It Administers

II.C.1. Prohibited Acts

The Federal Food, Drug, and Cosmetic Act is a law enforcement statute. The law prohibits specific acts or the causing thereof, such as:[7]

> The introduction or delivery for introduction into interstate commerce of any food, drug, device, or cosmetic that is adulterated or misbranded;
>
> The adulteration or misbranding of any food, drug, device, or cosmetic in interstate commerce; and
>
> The receipt in interstate commerce of any food, drug, device, or cosmetic that is adulterated or misbranded, and the delivery or proffered delivery thereof for pay or otherwise.

II.C.2. Adulteration

The act states that a device shall be deemed to be adulterated, in part (paraphrased):[8]

> If the methods used in, or the facilities or controls used for, its manufacture, packing, storage, or installation are not in conformity with applicable good manufacturing practices.
>
> It is a Class III device and is not the subject of a premarket approval application.

II.C.3. Misbranding

The act states that a device shall be deemed to be misbranded, in part (paraphrased):[9]

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[7] FDA applies regulatory procedures in determining whether a violation exists based upon the evidence it gathers, and when deciding the penalties or actions it may apply to remedy the violation. Penalties and violations are subject to the final concurrence by the court with jurisdiction. The violator is provided due process, e.g., to contest or appeal a charge of a FDCA violation.

[8] 21 U.S.C. §351(h).

[9] 21 U.S.C. §352.

> If its labeling is false or misleading in any particular.
>
> Unless its labeling bears (1) adequate directions for use; and (2) such adequate warnings against use in those pathological conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users, except that where any requirement of clause (1) of this paragraph, as applied to any drug or device, is not necessary for the protection of the public health, the Secretary shall promulgate regulations exempting such drug or device from such requirement;
>
> It is dangerous to health when used in the dosage or manner or with the frequency or duration prescribed, recommended, or suggested in labeling thereof;
>
> If a notice or other information respecting it was not provided as required by section 510(k); or
>
> For which there has been a failure or refusal to give required notification or to furnish required material or information such as section 519, medical device reports.

The act also states the following regarding misbranding:[10]

> If an article is alleged to be misbranded because the labeling or advertising is misleading, then in determining whether the labeling or advertising is misleading there shall be taken into account (among other things) not only representations made or suggested by statement, word, design, device, or any combination thereof, but also the extent to which the labeling or advertising fails to reveal facts material in the light of such representations or material with respect to consequences which may result from the use of the article to which the labeling or advertising relates under the conditions of use prescribed in the labeling or advertising thereof or under such conditions of use as are customary or usual.

The misbranding provisions of 21 USC §§352(q) and (r) relating to advertising for restricted devices do NOT apply to GYNEMESH PS because it is not a restricted device.[11]

[10] 21 USC §321(n).

[11] Devices must be designated by FDA as "restricted," either by a regulation promulgated under 21 USC §360j(e), or by a premarket approval application (PMA) approval order pursuant to 21 USC §360e(d)(1)(B)(ii)). Neither applies to the GYNEMESH PS device.

II.C.4. Tools Available to FDA to Enforce the Laws and Regulations It Administers

The FDA Regulatory Procedures Manual (RPM)[12] directs FDA personnel on internal procedures to be used in processing domestic and important regulatory and enforcement matters. While the RPM is intended mainly to provide guidance to FDA inspectors, investigators, and compliance officers, the document is useful to all of FDA and informative to the device industry.

The RPM describes the tools and actions FDA may take to help ensure compliance with the laws and regulations it administers. Those actions include (1) advisory, administrative, judicial and import actions, and (2) recall, emergency and other procedures. The key offices responsible for working together on these medical device actions and procedures include the Office of Compliance/CDRH, the Office of the Associate Commissioner for Regulatory Affairs, and the Office of Chief Counsel. Other FDA offices contribute only as needed.

According to the RPM, "When it is consistent with the public protection responsibilities of FDA and depending on the nature of the violation, it is FDA's practice to give individuals and firms an opportunity to take voluntary and prompt corrective action before it initiates an enforcement action. **Warning and Untitled Letters**, both advisory actions, are issued to achieve voluntary compliance and to establish prior notice. The use of these letters and the prior notice policy are based on the expectation that most individuals and firms will voluntarily comply with the law."

The FDA compliance office may exercise enforcement discretion when deciding whether to take enforcement action. Also, the RPM notes "there are instances when issuing a Warning Letter is not appropriate, and, as previously stated, a Warning Letter is not a prerequisite to taking enforcement action. Examples of situations where the agency will take enforcement action without necessarily issuing a Warning Letter include:

1. The violation reflects a history of repeated or continual conduct of a similar or substantially similar nature during which time the individual and/or firm has been notified of a similar or substantially similar violation;
2. The violation is intentional or flagrant;
3. The violation presents a reasonable possibility of injury or death;
4. The violations, under Title 18 U.S.C. 1001, are intentional and willful acts that once having occurred cannot be retracted. Also, such a felony violation does not require prior notice. Therefore, Title 18 U.S.C. 1001 violations are not suitable for inclusion in Warning Letters; and,
5. When adequate notice has been given by other means and the violations have not been corrected, or are continuing."

Relevant administrative actions include Section 305 notices

[12] FDA Regulatory Procedures Manual, http://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/ucm176446.htm.

(Citations), Section 305 meetings, administrative detention of devices, and civil money penalties (CMPs). **Detention and civil money penalties** are the most common actions taken. FDA may detain devices for a period of up to 30 calendar days if, during an inspection, the FDA has reason to believe the devices are adulterated or misbranded. The intent of administrative detention is to protect the public by preventing distribution or use of violative devices until FDA has had time to consider the appropriate action to take and, where appropriate, to initiate a regulatory action. The action of choice, in most cases, is a seizure. CMPs are monetary penalties that are assessed by FDA for violations of the law and regulations.

Some relevant judicial actions include seizure, injunction and prosecution. For a **seizure**, the United States of America, as Plaintiff, proceeds under the Supplemental Rules for Certain Admiralty and Maritime Claims (Supplemental Rules) by filing a Complaint for Forfeiture and obtaining a warrant for arrest of the device, directing the United States Marshal to seize (take possession or place in constructive custody of the court) the device. An **injunction** is a civil judicial process initiated to stop or prevent violation of the law, such as to halt the flow of violative products in interstate commerce, and to correct the conditions that caused the violation to occur. FDA can refer cases to the Department of Justice for **criminal prosecution.**

As part of import operations the government may **refuse to admit** devices for import and can **detain** devices upon import. Section 801(a) of the Federal Food, Drug, and Cosmetic Act directs the Secretary of the Treasury to issue a Notice of Refusal when it appears from examination of samples, or otherwise, that an imported shipment is in violation. This Section also orders the destruction of any such shipment refused admission, unless it is exported within 90 days of the date of the notice, or within such additional time as may be permitted pursuant to such regulations. FDA may refuse to admit devices based on information, *other than the results of examination of samples that causes an article to appear to violate the Act*.

Two common additional procedures are the **regulatory meeting** and "**It has come to our attention**" letters. A Regulatory Meeting is a meeting requested by FDA management, at its discretion, to inform responsible individuals or firms about how one or more products, practices, processes, or other activities are considered to be in violation of the law. FDA is not required to hold a Regulatory Meeting and, except for a few specifically defined areas, is not required to provide any other form of notice before taking an enforcement action. An "It has come to our attention letter" may be issued by OC where a potential violation has been observed and FDA requests information to assess the activity. It is not an advisory or enforcement letter.

Advisory, enforcement or other compliance actions are generally initiated by OC[13] or the Office of the Associate Commissioner for Regulatory Affairs based upon potential violations identified by many sources, e.g., inspections, public or industry complaints, FDA surveillance of public information, or internal agency referrals. Only

[13] The Office of In Vitro Diagnostic Devices and the Office of Surveillance and Biometrics can initiate compliance actions but the actions must be processed and approved through the Director of Compliance.

compliance and enforcement staff with the delegated responsibility can initiate, process or issue an enforcement or advisory action.

The Office of Compliance assesses internal agency referrals of a potential violation, e.g., a referral from ODE. The Office of Compliance's initial assessment includes, for example, a determination if the referral describes an activity that may be a violation, whether there is adequate documentation of the activity, and an analysis of the risk to the public health.

II.D. The Life Cycle of Medical Devices; Designing and Testing Medical Devices Prior to Marketing; Risk Management Throughout the Device Life Cycle

FDA, other global regulatory counterparts, and the device industry have characterized the development and marketing of a medical device as a life cycle. The cycle begins with the manufacturer developing a concept for a new or modified device, the cycle proceeds through design phases, the design is transferred to manufacturing, the product is manufactured and the device is placed on the market. The cycle is complete when the device becomes obsolete or if the device is modified.

The design controls provisions of the FDA Quality System regulation, 21 CFR §820.30, provide the requirements a device manufacturer must incorporate into its design and development procedures and processes. Design controls consist of requirements for (1) design and development planning, (2) design inputs, (3) design outputs, (4) design reviews (5) verifying that design outputs meet design inputs requirements (6) validating that the finished device meets defined user needs and intended uses, and (7) transferring the design to manufacturing. Documentation of design activities is captured in the Design History File. Design changes before implementation are a managed process with the need for review and approval of changes, verifications and revalidation of the design, when needed.

The Quality System regulation characterizes these and other quality requirements as basic requirements.[14] Industry standards and best practices serve to supplement the regulations, for example, by helping manufacturers determine the form and manner of recordkeeping indicated basically in regulation, and the procedures and specific policies the device manufacturer will follow when monitoring its devices while they are in the marketplace.

FDA recognizes that manufacturers are constantly developing new and improved devices and bringing these devices to the market even while prior versions of the same type of device continue to be legally marketed. The prior versions of devices remain on the market until the manufacturer decides to discontinue these previously marketed versions.

There is no requirement to tell FDA, e.g., in a PMA or 510(k) notification, about next generation devices in the development pipeline. However, manufacturers' design and quality data concerning devices being developed are subject to FDA inspection.

[14] 21 CFR §820.1(a).

Risk management is a life cycle process. Risk management is the systematic application of management policies, procedures, and practices to the tasks of identifying, analyzing, controlling, and monitoring risk.[15] Risk management is intended to be a framework within which experience, insight, and judgment are applied to successfully manage risk. Risk analysis, part of risk management, is required by the Quality System regulation as part of design validation.[16] Risk management also is an important industry standard and best practice, and FDA has recognized the international Risk Management standard, ISO 14971.[17] FDA has also cited ISO 14971 in guidance concerning benefit/risk determinations.[18]

Risk management by a manufacturer begins with the initial development of the design input requirements and assessment of risks known or anticipated at the initial stages of product design. In this way, unacceptable risks can be identified, to the degree possible, and managed earlier in the design process when changes are easier to make and less costly. Preliminary Hazard Analyses, Failure Modes and Effects Analyses (FMEAs),[19] Hazard and Operability Studies, Hazard Analyses and Critical Control Point, Fault Tree Analyses are examples of commonly used tools in the risk analysis process. These analyses are often contained in Risk Management Reports containing the risk assessment, risk control, residual risk and risk acceptability elements of the risk management process for a specific type of device.

Risk management is an iterative process. As the international risk management standard notes, the manufacturer should monitor production and post-production information for data and information that may affect the risk estimates.

Probability of event estimation, determination of probability levels and associated scores related to hazards are a part of risk analysis. ISO 14971:2007 states:[20]

> Seven approaches are commonly employed to estimate probabilities:
> -Use of relevant historical data
> -Prediction of probabilities using analytical or simulation techniques
> -Use of experimental data
> -Reliability estimates

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[15] See discussion of risk management in FDA Design Control Guidance, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070627.htm. The International Standards Organization (ISO) Standard 14971:2007 is commonly utilized to develop the processes and procedures associated with risk management activities.

[16] 21 CFR §820.30(g).

[17] ISO 14971 FDA recognition, http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/detail.cfm?standard__identification_no=30268.

[18] Factors to Consider When Making Benefit/risk Determinations in Medical Device PMAs, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm267829.htm.

[19] Device Design Safety Analyses are similar to FMEAs.

[20] ISO 14971:2007, Section D.3.2.2; Manufacturers sometimes use the probability cut points described in the standard when devising their risk procedures.

-Production data
-Post-production information
-Use of expert judgment

Severity of an event related to hazards is also a risk analysis factor. As with probability, for analysis purposes a manufacturer determines the levels of severity and how each level is defined.[21] A manufacturer assigns a score to each level.

Risk acceptability is typically displayed on a severity versus probability table with acceptable, unacceptable and as low as reasonably practicable regions in the table defined by the manufacturer. The ISO standard states that all risks should be reduced to the lowest level practicable by design, protective measures, or by providing information for safety.

Manufacturers often use risk priority numbers (RPN) in their risk analyses. The RPN is a value determined by multiplying scores of severity, probability, and detection. Risk reduction actions affect the RPN by lowering the RPN. Manufacturers define RPN cut-off values to prioritize risks and to help define acceptable risk levels.

If a residual risk is not acceptable, as determined by the manufacturer, after all practicable risk reduction measures have been applied, then the manufacturer conducts a risk/benefit analysis to determine if the residual risk is justified. The ISO standard provides that "experienced and knowledgeable individuals" make the risk/benefit decision.[22] These individuals may be, for example, medical staff.

II.E. Classification and Regulatory Paths to the Market

II.E.1. Classification

Classification is fundamental to FDA's regulation of medical devices. The act establishes three classes of devices, Class I, II, and III.[23] The act provides mandatory regulatory controls for each class to provide reasonable assurance of safety and effectiveness for devices within each class. Class I is subject to "General Controls" including, for example, adulteration and misbranding, registration and listing, adverse event reporting, and good manufacturing practice (quality system) requirements. In addition to General Controls, Class II devices are generally subject to defined regulatory "Special Controls" that may include, for example, a specific guidance document, or an additional labeling requirement. Class III devices are subject to Premarket Approval but also must meet General Controls.

FDA, based on the recommendations of panels of experts, was tasked with classifying all devices on the market on May 28, 1976, when the device amendments came into effect, into one of the three classes based upon the panels' assessments of safety and effectiveness of those devices. One exception is about a dozen types of devices that were regulated as drugs prior to May 1976 were by law considered Class III devices.

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[21] ISO 14971:2007, Section D.3.3.
[22] ISO 14971:2007, Section D.6.1.
[23] 21 USC §360c.

The remaining devices were grouped into generic types. Surgical mesh is one such type of device. The classifications for all the types of devices are detailed in 21 CFR, Parts 862-892. In 1982 an FDA panel proposed that surgical mesh be classified Class II (47 FR 2810). The classification for surgical mesh became final in 1988 (53 FR 23872).

For specific devices not on the market on May 28, 1976 the act provides that any device intended for human use which was not introduced or delivered for introduction into interstate commerce for commercial distribution before May 28, 1976 is classified in class III unless the device is found by FDA to be "substantially equivalent" to a type of device (a predicate device) classified into class I or II. FDA determines whether the new device is substantially equivalent to a predicate by its review of what the act describes as a "report" submitted to FDA preceding introduction of the device into interstate commerce. This "report" is the 510(k) notification.

II.E.2. Paths to the Market

There are two main regulatory paths to the market for medical devices. One path is FDA approval of a premarket approval application (PMA) for a Class III device[24] and the other is by FDA clearance of a premarket notification submission for a Class II device, commonly known as a 510(k) submission. Virtually all Class I devices and many Class II devices are exempt from the requirement to submit a 510(k) submission. The logical path, i.e., PMA or 510(k), for a manufacturer to consider for a new device depends mainly on whether there is an existing regulatory classification for a similar generic type of device. For example, there is a regulatory classification of Class II for the generic group "surgical mesh" based on the FDA panel recommendations in 1982.[25] Mesh devices used for prolpase surgery like GYNEMESH PS, are all a type of surgical mesh; therefore, the appropriate and logical path for a manufacturer to follow to obtain market clearance for a new pelvic mesh device generally would be to submit a 510(k) notification to FDA using a legally marketed predicate from the same classified surgical mesh group.

For the purposes of this report on GYNEMESH PS, I will discuss the 510(k) submission path to clearance for marketing.

The act describes the form and manner of the "report", aka, 510(k) notification.[26] It provides, in part, that each person who is required to register and who proposes to begin the introduction or delivery for introduction into interstate commerce for commercial distribution of a device intended for human use shall, at least ninety days before making such introduction or delivery, "report" to FDA (in such form and manner as FDA shall by regulation prescribe) (1) the class in which the device is classified under Section 360c and (2) action taken by such person to comply with requirements under 21 USC §360d (standards) or Section 360e (premarket approval) which are applicable to the device. These original fundamental provisions of a 510(k) "report" have been

[24] PMAs for pre-amendment Class III devices are not required until FDA publishes a final rule requiring PMAs. Until then an applicant for an equivalent device must submit via the 510(k) process.
[25] 21 CFR §880.3300.
[26] 21 U.S.C. §360(k).

expanded, defined, and enriched in several amendments to the act after 1976.

The term “substantially equivalent”, which I have noted above, is at the core of classification by means of a 510(k) submission. An amendment to 360c(i) of the act incorporated a definition of this term that FDA had previously included in guidance. According to the act, “substantially equivalent” or “substantial equivalence” means that the new device has the same intended use as the predicate device and the same technological characteristics, or if it does not have the same characteristics then information submitted demonstrates that the new device is as safe and effective as the predicate and does not raise different questions of safety and effectiveness than the predicate device. The FDA review criteria discussed below for a 510(k) submission incorporate this statutory provision and expand upon it.

According to a recent FDA guidance, safety and effectiveness is an inherent part of FDA's determination of substantial equivalence.[27] The guidance states, "The 510(k) review standard (substantial equivalence of a new device to a legally marketed (predicate) device) differs from the PMA review standard (reasonable assurance of safety and effectiveness). The 510(k) review standard is comparative, whereas the PMA standard relies on an independent demonstration of safety and effectiveness. Nonetheless, the principles of safety and effectiveness underlie the substantial equivalence determination in every 510(k) review."

This is especially true where the new device is “substantially equivalent” to a device in a group that has been classified into Class II based on the recommendations of an FDA advisory panel.

II.E.3. Premarket Notification Submissions

The 510(k) regulation, 21 CFR §807.81, describes when a 510(k) is required. In part, a 510(k) is required for a device being marketed for the first time or for a marketed device that is to be significantly changed or modified in design, components, method of manufacture, or intended use.[28]

The regulation under 21 CFR §807.87 also describes information required in a 510(k). The 510(k) must include, in part: labels, labeling, and advertisements sufficient to describe the device, its intended use, and the directions for its use; comparisons to other legally marketed devices; and any other information the FDA needs to determine substantial equivalence.[29] FDA’s review of 510(k) data and information is rigorous and thorough.

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[27] Guidance for Industry and Food and Drug Administration Staff - The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)], http://www.fda.gov/downloads/medicaldevices/.../ucm284443.pdf.

[28] Many Class I and some Class II devices are exempt from 510(k) notification requirements.

[29] “[A]ny other information” may include, for example, preclinical or clinical data, or revised labeling.

There is ample FDA guidance pertaining to 510(k)s. Some FDA guidance applies to the submission process in general[30] while product-specific guidance, if available, provides more details on format and content for a 510(k). The details may include standards that should be applied, specific tests and outputs, and specific labeling recommendations.

Guidance is not mandatory. FDA Good Guidance Practices (GGPs) state "You (for instance a manufacturer) may choose to use an approach other than the one set forth in a guidance document. However, your alternative approach must comply with the relevant statutes and regulations."[31] GGPs also state "Although guidance documents do not legally bind FDA, they represent the agency's current thinking. Therefore, FDA employees may depart from guidance documents only with appropriate justification and supervisory concurrence."

FDA issued guidance for surgical mesh in 1999, which is the generic type of device under which pelvic mesh is classified.[32] The guidance recommends that 510(k)s for surgical mesh include, in part: a summary of safety and effectiveness or a statement that such information is available upon request, specification of all material components of the device, manufacturing information, packaging information, product characterization, and labeling. The document states a final consideration that additional information may be required as technological advances continue but it does not specifically identify the need for clinical data.

There are three types of 510(k) submissions including traditional, special and abbreviated. Traditional submissions can be used under any circumstances and include all information typically required for a 510(k) submission. Abbreviated submissions may include some abbreviated information compared to a traditional submission because this submission method relies on "declarations of conformity" to FDA-recognized standards the manufacturer used when designing and/or manufacturing the device. A special 510(k) may be used when a manufacturer wishes to significantly modify one of its own legally marketed devices. These three processes are described in FDA guidance.[33]

From its review of a 510(k) submission, the FDA may determine, by order, that a 510(k) submission is substantially equivalent (SE), SE with limitations,[34] not substantially equivalent (NSE), or that

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[30] 510(k) Submission Process, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/ucm070201.htm.

[31] 21 CFR §10.115.

[32] Guidance for Industry and/or for FDA Reviewers/Staff and/or Compliance - Guidance for the Preparation of a Premarket Notification Application for a Surgical Mesh, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073790.htm.

[33] The New 510(k) Paradigm: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080187.htm.

[34] Determination of Intended Use for 510(k) Devices; Guidance for CDRH Staff (Update to 98-1),

additional information is needed to render a decision (AI). FDA considers a device that it finds SE by means of a 510(k) to be "cleared." A device is "approved" only by an FDA approval order for a premarket approval application.

Prior to the Safe Medical Devices Act of 1990 (SMDA)[35] manufacturers could go to market after 90 days of submission of the 510(k) unless FDA intervened beforehand by either calling the submitter to "hold" the review clock, or by issuing an Additional Information (AI) or Not Substantially Equivalent (NSE) letter. Now, FDA must issue an order for a 510(k) declaring the device equivalent before the device may be marketed.

The current language in the standard FDA Additional Information (AI) letters that "You may not market this device until…you have received a letter from FDA allowing you to do so" was included in the form AI letter after SMDA in 1990. FDA may apply enforcement discretion regarding this provision in certain cases.[36] The AI letter is also an administrative letter issued by the Office of Device Evaluation simply to convey to the manufacturer the information ODE needs to complete its review. It is not an enforcement action.

FDA notes that there are "…many changes in the evolution of a device."[37] When making changes to a marketed device a manufacturer determines that a new 510(k) is needed according to regulation when:

> the device is one that the person currently has in commercial distribution or is reintroducing into commercial distribution, but that is about to be significantly changed or modified in design, components, method of manufacture, or intended use. The following constitute significant changes or modifications that require a premarket notification:
> (i) A change or modification in the device that could significantly affect the safety or effectiveness of the device, e.g., a significant change or modification in design, material, chemical composition, energy source, or manufacturing process.
> (ii) A major change or modification in the intended use of the device.[38]

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http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm082162.htm.

[35] SMDA, The Safe Medical Devices Act of 1990 (P.L. 101-629), which amended the FFD&C Act (21 U.S.C. 201 et seq.), was signed into law on November 28, 1990.

[36] Two cases where enforcement discretion has been applied include (1) a device is modified after a recall and continues to be marketed and then changes to the device are submitted in a 510(k). (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080297.htm), and (2) submission of a 510(k) after a device has been marketed when FDA requests voluntary submission and ODE makes an enforcement referral to OC, e.g., a manufacturer makes a change to a device it deemed not significant but is later deemed significant by FDA.

[37] FDA Guidance: Deciding When to Submit a 510(k) for a Change to an Existing Device.

[38] 21 CFR §807.81(3).

The FDA guidance document "Deciding When to Submit a 510(k) for a Change to an Existing Device (K97-1), January 10, 1997"[39] was developed to help assist manufacturers in deciding when a change to a device was "significant" or "major." FDA notes in the guidance "To be certain that a decision on when to submit a 510(k) is correct, one would probably need to enumerate all device types and all potential types of changes and then match each combination of device and change with a decision. Given that there are thousands of individual device types and possibly tens or hundreds of enumerable changes, this would be an impossible task. Furthermore, the resultant guidance would fill volumes, would probably be difficult to use, and would be unlikely to keep pace with an ever-changing technology."

While the guidance tries to provide general guidance on making decisions regarding changes to devices it is clear that FDA relies heavily on manufacturer compliance with the Quality System regulation as the fundamental means of ensuring device safety and effectiveness. The guidance states, "For many types of changes to a device, it may be found that a 510(k) is not necessary, and the Agency may reasonably rely on good manufacturing practices (either as implemented under the 1978 GMP or the Quality Systems regulation) to continue to assure the safety and effectiveness of the changed device. This reliance is enhanced when manufacturers document their decision-making based on their testing results or other design validation criteria." Also, manufacturers "must have a process in place to demonstrate that the manufactured device meets the change in design specifications (or the original specifications, if no change was intended). They must keep records, and these records must be made available to an FDA inspector." The guidance states, "No matter how carefully this guidance is applied, there will still be decisions in a "gray area" <u>that manufacturers will have to make</u> (emphasis added)."[40] Manufacturers are encouraged, <u>but not required</u>, to contact FDA when the proposed change is not addressed in the guidance flowcharts. In fact, in my experience it was rare that a manufacturer called my division in ODE or the Office of Compliance to request an opinion on a change to a marketed device.

It was reported in 2008 that there are more than 20,000 companies worldwide and 80,000 brands and models of devices.[41] So, based on the fact that FDA notes there are numerous changes with devices, there are probably tens of thousands of changes to devices in any given year. However, for example, there were only 3363 510(k)s submitted in 2008, and only 653 were special 510(k)s.[42] Various conclusions could be drawn from this data but it is evident that relatively few changes to marketed devices result in new 510(k) submissions.

FDA proposed a revision to the K97-1 guidance in 2011 based upon its current thinking about changes to devices. Congress rebuked FDA due to the content of the draft guidance, requiring the following

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[39] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080235.htm.

[40] Ibid.

[41] Advamed. The 510(k) Process: The Key to Effective Device Regulation, 8/19/08.

[42] ODE Annual Report 2008. Special 510(k)s are meant for changes to marketed devices.

extraordinary actions in the Food and Drug Safety and Innovation Act (FDSIA):[43]

> Not later than 18 months after the date of enactment of this paragraph, the Secretary shall submit to the Committee on Energy and Commerce of the House of Representatives and the Committee on Health, Education, Labor, and Pensions of the Senate a report regarding when a premarket notification under subsection (k) should be submitted for a modification or change to a legally marketed device. The report shall include the Secretary's interpretation of the following terms: 'could significantly affect the safety or effectiveness of the device', 'a significant change or modification in design, material, chemical composition, energy source, or manufacturing process', and 'major change or modification in the intended use of the device. The report also shall discuss possible processes for industry to use to determine whether a new submission under subsection (k) is required and shall analyze how to leverage existing quality system requirements to reduce premarket burden, facilitate continual device improvement, and provide reasonable assurance of safety and effectiveness of modified devices.

The FDSIA also states:

> The Secretary shall withdraw the Food and Drug Administration draft guidance entitled 'Guidance for Industry and FDA Staff— 510(k) Device Modifications: Deciding When to Submit a 510(k) for a Change to an Existing Device', dated July 27, 2011, and shall not use this draft guidance as part of, or for the basis of, any premarket review or any compliance or enforcement decisions or actions.

Congress directed FDA to keep in place the K97-1 guidance until Congress concurred with any new FDA guidance on the issue as noted above. FDA submitted a report to Congress on its intentions regarding this guidance and withdrew the draft guidance on July 17, 2012.[44,45]

The upshot of these recent mandatory statutory provisions related to modifications to marketed devices and the need to submit a new 510(k) is that Congress was telling FDA (1) there is a need for industry and FDA consensus on the definition of terms used in the 510(k) regulation related to modification of devices, suggesting even the existing K97-1 guidance and processes are unsatisfactory, (2) Congress will not tolerate a stringent or expanded interpretation of when a 510(k) is needed for a change to a device, as was the case in the withdrawn 2011 guidance, and (3) compliance with the Quality System regulation should be used as a foundation for "reasonable assurance of safety and

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[43] http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDASIA/ucm20027187.htm.

[44] Withdrawal of draft guidance, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm265274.htm.

[45] http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/UCM387121.pdf.

effectiveness" of modified devices.

In the recent FDSIA amendment Congress uses the terms "reasonable assurance of safety and effectiveness" related to regulation of modified 510(k) devices and not "substantial equivalence" thus further blurring the line between premarket approval and premarket notification.

II.E.4. How FDA Determined Substantial Equivalence Prior to July 28, 2014

FDA premarket submission reviewers used the decision flowchart first described in a 1986 FDA guidance document when determining substantial equivalence of devices such as ETHICON GYNEMESH PS and when documenting their decision.[46] As noted above, the substantial equivalence decision process contained in FDA guidance was incorporated into the act.

The 1986 guidance document describes the key decision elements in determining substantial equivalence, as follows:

> *Thus, as a matter of practice, CDRH generally considers a device to be SE to a predicate device if, in comparison to the predicate device:*
>
> *the new device has the same intended use (as discussed below); and,*
>
> *the new device has the same technological characteristics, (i.e., same materials, design, energy source, etc.); or, it has new technological characteristics that could not affect safety or effectiveness; or*
>
> *it has new technological characteristics that could affect safety or effectiveness, and*
>
> *-- there are accepted scientific methods for evaluating whether safety or effectiveness has been adversely affected as a result of the use of new technological characteristics; and*
>
> *-- there are data to demonstrate that the new technological features have not diminished safety or effectiveness.*

The document describes decision aspects when determining whether the new device has the same intended use as the predicate as follows:

> *While a new device must have the same intended use as a predicate device in order to be SE, the Center does not require that a new device be labeled with precise therapeutic or diagnostic statements identical to those that appear on predicate device labeling in order for the new device to have the same intended use. Label statements may vary. Certain elements of a predicate device's labeled indication may not be critical to its intended therapeutic, diagnostic, prosthetic, surgical, etc., use. The Center's scientific expertise enables it to exercise considerable discretion in construing intended uses in the labeling and*

[46] Guidance on the CDRH Premarket Notification Review Program 6/30/86. (K86-3), 510(k) Memorandum #K86-3: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm081383.htm. FDA updated this flowchart in 2014.

> *promotional materials for predicate and new devices. Thus, a new device with the same intended use as a predicate device may have different specific indication statements, and, as long as these label indications do not introduce questions about safety or effectiveness different from those that were posed by the predicate device's intended use, the new device may be found SE.*
>
> *For the purposes of determining whether or not the new device has the same intended use as a predicate device, the Center assesses any difference in label indications in terms of the safety and effectiveness questions they may raise. The Center considers such points as physiological purpose (e.g. removes water from blood, transports blood, cuts tissue), condition or disease to be treated or diagnosed, professional or lay use, parts of the body or types of tissue involved, frequency of use, etc. If a new device is determined to have the same intended use, the Center may then proceed to determine whether or not it is substantially equivalent. (Devices which do not have the same intended use cannot be substantially equivalent.)*

For technological differences the guidance states:

> *Thus, from a scientific perspective, to determine which technological changes are consequential, the Center considers whether:*
>
> - *the new device poses the same type of questions (emphasis added) about safety or effectiveness as a predicate device.;*
> - *there are accepted scientific methods for evaluating whether safety or effectiveness has been adversely affected as a result of the use of new technological characteristics; and*
> - *there are data to demonstrate that new technological characteristics have not diminished safety or effectiveness*

In terms of performance data the guidance notes:

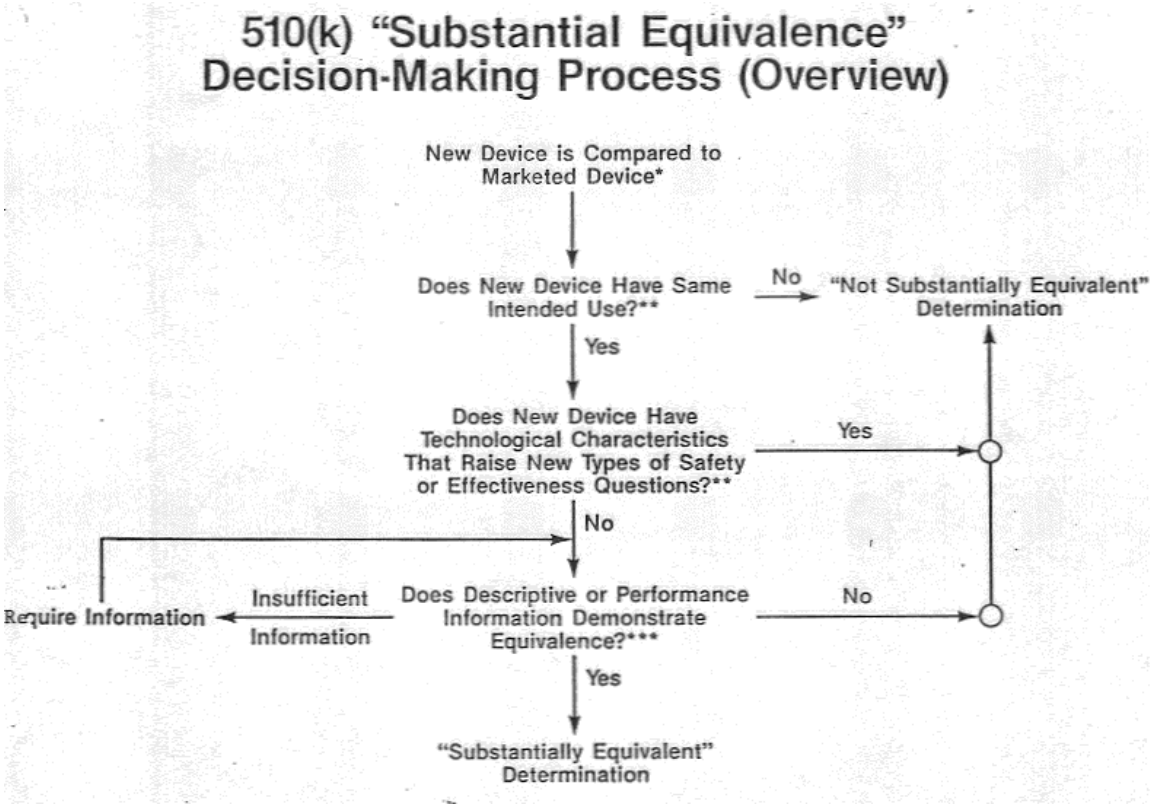
> *Typically, 510(k) provides descriptive and testing data that compares the new device to another marketed device within the type, but does not necessarily compare the new device directly to a predicate device. In these cases, the Center can rely, as necessary, on performance data appearing in previously reviewed 510(k) files, in Center classification files, or in the literature, to determine that the device is not only comparable to another marketed device within its type, but is also SE to a predicate device.*

FDA's consideration of substantial equivalence evolved over time to incorporate the consideration of a "reference device" when assessing performance data.[47] A submitter may use a reference device, which is a legally marketed device that has a different intended use or different technological characteristics that raise different questions of safety and effectiveness, to address specific scientific questions or performance characteristics for a new device. For example, a reference

[47] The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications, http://www.fda.gov/downloads/medicaldevices/.../ucm284443.pdf.

device may be useful as supportive evidence of the safety of a material used in a new device.

A summary version of the decision tree taken from the 1986 guidance and used by FDA and industry for the determination of substantial equivalence and documentation of the decision is as follows:[48]



II.E.5. Significant Changes to 510(k)s Since 1976 Relating to the Evaluation of Safety and Effectiveness; Assessment of the 510(k) Program by the Institute of Medicine Rejected by FDA

The 510(k) submission process has significantly evolved since 1976 due to statutory, regulatory and procedural changes. The 510(k) process is a considerable hurdle to manufacturers seeking to market a new device. Coupled with the 510(k) process, and equally applicable to PMA devices, is the need for manufacturers to comply with the quality system regulation. The quality system regulation provides requirements spanning the life cycle of a medical device.

The first significant change to the act after 1976 regarding 510(k)s

[48] An updated chart posted by FDA and used for FDA and industry documentation purposes. (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM081395.pdf) has essentially the same elements, but expands the considerations regarding the need for performance data.

was the Safe Medical Device Act of 1990 (SMDA).[49] SMDA increased the authority of FDA and the requirements for manufacturers, morphing Class II determinations into decisions about safety and effectiveness by requiring FDA to make decisions on the reasonable assurance of safety and efficacy of the device. The definition of "substantial equivalence" was incorporated into the act, as noted above in this report. Additionally, "Special Controls" replaced "Performance Standards" for Class II devices as noted earlier in this report. Further, a summary of safety and effectiveness was required in a 510(k), preproduction design controls were now regulated, FDA had to issue a 510(k) equivalence order before a device submitted under a 510(k) could be marketed, and correction and removal reports to FDA were required. Also, the relatively few 510(k)s for Class III devices had to now include a summary of adverse data relating to the safety and effectiveness of the device.

The next significant change was the FDA Modernization Act of 1997.[50] FDAMA focused FDA resources on those devices presenting the most risk. FDAMA instituted "Good Guidance Practices" to strengthen the development and vetting of documents to the public. The "least burdensome" principles were also added. In a guidance document[51] FDA defined least burdensome as "a successful means of addressing a premarket issue that involves the most appropriate investment of time, effort, and resources on the part of industry and FDA."

The Medical Device User Fee Act of 2002 (MDUFMA) was enacted "in order to provide the Food and Drug Administration (FDA) with the resources necessary to better review medical devices, to enact needed regulatory reforms so that medical device manufacturers can bring their safe and effective devices to the American people at an earlier time…"[52] The 2007 amendments to the act allowed third party review of some submissions.[53]

Dr. Jeff Shuren, Director of CDRH, stated in a press release on July 29, 2011:

> "We...agree that the public should continue to feel confident in the medical devices on the market today. Medical devices in the U.S. have a strong track record of safety and effectiveness. The 510(k) program has helped support a robust medical device

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[49] The Safe Medical Devices Act of 1990 (P.L. 101-629), which amended the FFD&C Act (21 U.S.C. 201 et seq.), was signed into law on November 28, 1990.

[50] FDAMA, http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDAMA/default.htm.

[51] The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Final Guidance for FDA and Industry, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm085994.htm.

[52] MDUFA, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFMA/ucm109149.htm

[53] FDAAA, http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/FullTextofFDAAALaw/default.htm.

> industry in the U.S. and has helped bring lower-risk devices to market for the patients who need them.
>
> FDA believes that the 510(k) process should not be eliminated but we are open to additional proposals and approaches for continued improvement of our device review programs."[54]

As I note above, on July 28, 2014 FDA posted new guidance regarding the evaluation of substantial equivalence in premarket notifications stating the principles of safety and effectiveness underlie the determination of equivalence. FDA also posted draft guidance on benefit-risk factors to consider when determining substantial equivalence in premarket notifications.[55] It is clearly evident that the 510(k) process is and will continue to be a viable path to the determination by FDA of the reasonable assurance of safety and effectiveness for new medical devices not subject to PMAs.

II.F. Postmarket Surveillance, Monitoring Device Experience: Complaints, Medical Devices Reports, Corrective and Preventive Actions

Once a device is marketed manufacturers and FDA continue to monitor the device's safety and effectiveness. Three regulatory life cycle activities associated with postmarket surveillance are closely linked and describe the basic requirements of the system for receiving, assessing and taking appropriate action based on postmarket signals. These activities include complaint handling, medical device reports, and corrective and preventive actions. Industry standards and best practices play an important role in formulating the documentation, policies and procedures for these quality management activities.

As required by 21 CFR §820.198, Complaint Files, each manufacturer shall establish and maintain procedures for receiving, reviewing, and evaluating complaints by a formally designated unit. Such procedures shall ensure that the manufacturer (1) processes all complaints in a uniform and timely manner, and (2) evaluates all complaints to determine whether any complaints represent an event, which is required to be reported to FDA under part 803, Medical Device Reporting. The manufacturer is required to evaluate complaints and make investigations as needed. Any complaint involving the possible failure of a device, labeling, or packaging to meet any of its specifications shall be reviewed, evaluated, and investigated, unless such investigation has already been performed for a similar complaint and another investigation is not necessary.

The medical device reporting regulation, 21 CFR Part 803, establishes the requirements for medical device reporting of events identified in the complaint process for device user facilities, manufacturers, and importers. A manufacturer or importer must report to FDA deaths and serious injuries its device has or may have *"caused or contributed"* to

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[54] Press release, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2011/ucm265908.htm.

[55] Benefit-Risk Factors to Consider When Determining Substantial Equivalence in 510(k)s, http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm282958.htm.

and, certain device malfunctions, and the manufacturer or importer must establish and maintain adverse event files. A manufacturer must also submit specified follow-up.

The term "caused or contributed" by regulation means that a death or serious injury was or may have been attributed to a medical device, or that a medical device was or may have been a factor in a death or serious injury, including events occurring as a result of failure, improper or inadequate design, manufacture, labeling, or user error.[56]

According to FDA, "(MDR) Reports are not required when there is information that would cause a person who is qualified to make a medical judgment (e.g., a physician, risk manager, or biomedical engineer) to reach a reasonable conclusion that a device did not cause or contribute to an MDR reportable event. Information that leads to the conclusion that an event is not reportable must be retained in the MDR event files for the time periods specified in Sec. 803.18."[57] This provision is part of the MDR regulation.[58]

FDA posts MDRs on the MAUDE database.[59] FDA states on its web site, "MAUDE data is not intended to be used either to evaluate rates of adverse events or to compare adverse event occurrence rates across devices."

In Subpart J of 21 CFR §820, Corrective and Preventive Action,[60] also known as CAPA, it is required that manufacturers establish and maintain procedures for implementing corrective and preventive action. The procedures shall include requirements, in part, for analyzing processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of product that do not meet a specific requirement (i.e., a nonconformity), or other quality problems.

The manufacturer must investigate the cause of nonconformities relating to product, processes, and the quality system; identify the action(s) needed to correct and prevent recurrence of nonconforming product and other quality problems; verify or validate the corrective and preventive action to ensure that such action is effective and does not adversely affect the finished device; implement and record changes in methods and procedures needed to correct and prevent identified quality problems; and ensure that information related to quality problems or nonconforming product is disseminated to those directly responsible.

So, for example, if a complaint is received concerning a death or injury then the manufacturer is obligated to assess it and determine if an investigation is warranted and whether an MDR report must be submitted. Steps may be taken to mitigate the event and/or likelihood of the event reoccurring based on reestablished CAPA procedures.

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[56] 21 CFR §803.3.
[57] FR Notice, Vol.60, No.237 (12/11/95), comment 11.
[58] 21 CFR §803.20(c)(2).
[59] MAUDE, http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.CFM.
[60] 21 CFR §820.100.

Outputs of decision-making in CAPA may be a recall, labeling changes, notices to users, or other actions.

FDA inspects manufacturers to help ensure compliance with 21 CFR Parts 820 and 803, including the complaint, MDR, and CAPA processes. It uses the Quality System Inspection Technique (QSIT) guidance[61] for FDA investigators as one basis for evaluating these processes.

II.G. Medical Device Labeling Regulations

The term "labeling" means all labels and other written, printed or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article.[62] The term "label", in part, means a display of written, printed, or graphic matter upon the immediate container of any article.[63] Labeling includes important information to the end user to enable him or her to use the product safely and effectively for the indications listed therein.

Labeling requirements for medical devices are provided in 21 CFR Part 801, Labeling. The labeling regulation describes the form and content of labeling, provisions for devices labeled for over the counter use, and specific statements for certain devices. Adequate directions for use, 21 CFR §801.5, provide labeling requirements for devices intended for lay use, i.e., over-the-counter product.

II.G.1. Content and Format of Prescription Labeling

An exemption from adequate directions for lay use is provided for prescription devices. As noted in the regulation:

> *A device which, because of any potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use is not safe except under the supervision of a practitioner licensed by law to direct the use of such device, and hence for which "adequate directions for use" cannot be prepared, shall be exempt from section 502(f)(1) of the act if all the following conditions are met:*
>
> *(a) The device is:*
>
> *(1)(i) In the possession of a person, or his agents or employees, regularly and lawfully engaged in the manufacture, transportation, storage, or wholesale or retail distribution of such device; or*
>
> *(ii) In the possession of a practitioner, such as physicians, dentists, and veterinarians, licensed by law to use or order the use of such device; and*
>
> *(2) Is to be sold only to or on the prescription or other order of such practitioner for use in the course of his professional practice.*
>
> *(b) The label of the device, other than surgical instruments, bears:*

[61] http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074883.htm.
[62] Section 201(m) of the act (21 USC §321(m)).
[63] Section 201(k) of the act (21 USC §321(k)).

(1) The statement "Caution: Federal law restricts this device to sale by or on the order of a ____", the blank to be filled with the word "physician", "dentist", "veterinarian", or with the descriptive designation of any other practitioner licensed by the law of the State in which he practices to use or order the use of the device; and

(2) The method of its application or use.

(c) Labeling on or within the package from which the device is to be dispensed bears information for use, including indications, effects, routes, methods, and frequency and duration of administration, and any relevant hazards, contraindications, side effects, and precautions under which practitioners licensed by law to administer the device can use the device safely and for the purpose for which it is intended, including all purposes for which it is advertised or represented: Provided, however, that such information may be omitted from the dispensing package if, but only if, the article is a device for which directions, hazards, warnings, and other information are commonly known to practitioners licensed by law to use the device. Upon written request, stating reasonable grounds therefore, the Commissioner will offer an opinion on a proposal to omit such information from the dispensing package under this proviso.

(d) Any labeling, as defined in section 201(m) of the act, whether or not it is on or within a package from which the device is to be dispensed, distributed by or on behalf of the manufacturer, packer, or distributor of the device, that furnishes or purports to furnish information for use of the device contains adequate information for such use, including indications, effects, routes, methods, and frequency and duration of administration and any relevant hazards, contraindications, side effects, and precautions, under which practitioners licensed by law to employ the device can use the device safely and for the purposes for which it is intended, including all purposes for which it is advertised or represented. This information will not be required on so-called reminder--piece labeling which calls attention to the name of the device but does not include indications or other use information.

(e) All labeling, except labels and cartons, bearing information for use of the device also bears the date of the issuance or the date of the latest revision of such labeling.

II.G.2. Definitions of Intended Use, Indications, Contraindications, Warnings and Precautions

Intended Use: FDA regulations under 21 CFR §801.4 define the term "intended use" as follows:

The words intended uses or words of similar import in §§ 801.5, 801.119, and 801.122 refer to the objective intent of the persons legally responsible for the labeling of devices. The intent is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives. It may be shown by the

> *circumstances that the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised. The intended uses of an article may change after its manufacturer has introduced it into interstate commerce. If, for example, a packer, distributor, or seller intends an article for different uses than those intended by the person from whom he received the devices, such packer, distributor, or seller is required to supply adequate labeling in accordance with the new intended uses. But if a manufacturer knows, or has knowledge of facts that would give him notice that a device introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it, he is required to provide adequate labeling for such a device which accords with such other uses to which the article is to be put.*

Indications: The term "indications" is not defined in the medical device labeling regulation, 21 CFR Part 801. In 21 CFR §814.209(b)(3)(i), Indications for Use is stated as:

> *A general description of the disease or condition the device will diagnose, treat, prevent, cure, or mitigate, including a description of the patient population for which the device is intended.*

Device Labeling Guidance[64] states the Indications for Use identifies the target population in a significant portion of which sufficient valid scientific evidence has demonstrated that the device as labeled will provide clinically significant results and at the same time does not present an unreasonable risk of illness or injury associated with the use of the device. As appropriate, the labeling should state that the device (trade name) is "indicated" or "intended for use"

> (1) in the treatment, mitigation, prevention or diagnosis of a recognized disease or condition or an important manifestation of a disease or condition; and/or,
> (2) in the relief or mitigation of symptoms associated with a disease or condition; and/or,
> (3) as an aid or adjunct to a mode of therapy or diagnosis.

Contraindications: As suggested in the labeling guidance this section describes situations in which the device should not be used because the risk of use clearly outweighs any possible benefit. Known hazards and not theoretical possibilities are to be listed.

Warnings: As suggested in the labeling guidance this section describes serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. Labeling should include an appropriate warning if there is reasonable evidence of an association of a serious hazard with the use of the

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[64] Device Labeling Guidance #G91-1 (blue book memo), http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm081368.htm. This guidance is based on drug regulations. Device regulations note the terms any "hazards" and "side effects" while "adverse reactions" in the guidance is a term used for drugs. There are no device regulations other than 21 CFR Part 801 describing the content requirements of labeling.

device. A causal relationship need not have been proved.

A warning is appropriate when the device is commonly used for a disease or condition for which there is a lack of valid scientific evidence of effectiveness for that disease or condition and such usage is associated with a serious risk or hazard.

Precautions: As suggested in the labeling guidance this section includes information regarding any special care to be exercised by the practitioner and/or patient for the safe and effective use of the device.

Adverse Reactions: As suggested in the labeling guidance an adverse reaction is an undesirable effect, reasonably associated with the use of the device that may occur as part of the effect of the device or may be unpredictable in its occurrence.

According to the drug regulation-based FDA guidance this section includes all adverse reactions reasonably associated with the use of the device, including those mentioned in the "Contraindications", "Warnings" and "Precautions" sections of the labeling. The listing of the adverse reactions should be followed, if appropriate, by statements directing the reader to other sections of the labeling for additional information regarding these adverse reactions and any steps that should be taken.

II.G.3. Promotion and Advertising

The term "promotion" is not defined in the act or device regulations. Promotion is a form of advertisement by common definition.[65]

There are some rules on device advertising in the act. As noted earlier in this report, 21 USC §§352(q) and (r) provide prohibitions on restricted device advertising. However, surgical mesh such as the ETHICON GYNEMESH PS device is not a restricted device.[66] FDA has authority to find device labeling false and misleading. Misleading labeling and advertising is defined under 21 USC §321(n). There are no medical device advertising regulations as there are for drugs. Advertising regulations pertaining to drugs, 21 CFR Part 202, are unenforceable for devices.

In my experience heading the Office of Compliance for devices the characterization of device advertising as labeling is typically unsuccessful in enforcement actions when there is no physical association of the device with the advertisement, i.e., it does not accompany the device. A 70-year-old appellate court case decision referenced by FDA guidance discussed the connection between labeling and advertising.[67] However, this was a case against a drug manufacturer and the case predated drug-advertising rules. The manufacturer claimed that circulars accompanying the drug were advertising and not labeling.

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[65] www.merriam-webster.com.

[66] Devices have been designated by FDA as "restricted," either by regulation promulgated under 21 USC 360j(e), or by premarket approval application (PMA) approval order pursuant to 21 USC §360e(d)(1)(B)(ii).

[67] United States v. Research Laboratories, inc., 126 F.2d 42, 1942, U.S. App. LEXUS 4060.

The printed advertising in this case accompanied the drug and, not surprisingly, was deemed to be labeling by the court.

The Federal Trade Commission has authority for advertising of devices that are not restricted devices while FDA exercises its authority over restricted device advertising.[68]

II.G.4. False and Misleading Device Labeling

A device is misbranded if its label "is false or misleading in any particular."[69] The act also states "If an article is alleged to be misbranded because the labeling or advertising is misleading, then in determining whether the labeling or advertising is misleading there shall be taken into account (among other things) not only representations made or suggested by statement, word, design, device, or any combination thereof, but also the extent to which the labeling or advertising fails to reveal facts material in the light of such representations or material with respect to consequences which may result from the use of the article to which the labeling or advertising relates under the conditions of use prescribed in the labeling or advertising thereof or under such conditions of use as are customary or usual."[70] There are misbranding provisions for only restricted device advertising. Drug labeling or advertising laws and regulations cannot be applied to misbranding for devices or enforced for devices.

FDA has previously issued guidance concerning false or misleading labeling[71] but this Device Advice guidance is not an enforcement guidance issued by the Office of Compliance or FDA Office of the Chief Counsel. The Device Advice guidance is not enforceable except where it refers to statute or regulation.

II.G.5. Patient Labeling

There is no general FDA regulatory requirement that a manufacturer must provide patient labeling for prescription devices, nor are there mandatory stipulations on the content and format of patient labeling.[72] FDA can require patient labeling for a specific device either as a condition of approval in a PMA approval order,[73] as part of a Class II device special controls guidance document,[74] or otherwise by a device-specific labeling regulation.[75] There are no such requirements for pelvic mesh devices.

Manufacturers, who are not required to provide patient labeling, as is

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[68] http://www.fda.gov/NewsEvents/Testimony/ucm096272.htm.
[69] 21 USC §352(a).
[70] 21 USC §321(n).
[71] Device Advice – Labeling Requirements:Misbranding.
[72] 21 CFR §801.109(d), labeling other than IFUs, can be interpreted to mean an IFU or similar information should be attached to any patient labeling.
[73] 21 CFR §814.44(e).
[74] General and Special Controls, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/GeneralandSpecialControls/default.htm#class_2.
[75] 21 CFR Part 801, Subpart H.

the case for surgical mesh,[76] do so voluntarily on their own initiative in keeping with industry standards and best practices for many types of devices. Patient brochures, patient directed circulars or handouts, leaflets, videos, or information sheets intended for and made available to or provided to the patient constitute types of patient labeling.

FDA posted guidance on patient labeling in 2001.[77] The guidance describes suggested content and formatting of patient labeling. Risk/benefit information is addressed in the guidance. In regard to warnings it states, "Including too many warnings and precautions, over-warning, dilutes the strength of all of the hazard alerts. We recommend that writers use care in what is designated as a warning or precaution. Careless designation can have the same diluting effect as over-warning." FDA held a public workshop on September 29 and 30, 2015, to discuss issues associated with the development and use of medical device patient labeling.[78]

In regard to adverse effects the guidance states, "When appropriate, provide information about any adverse events. Devices whose applications are supported by clinical trials will have data about adverse events that occurred during these trials and that may be of value to the device user. Other devices may have adverse event data from other sources, e.g., published literature or experience with similar devices. The detail in and the need to include an Adverse Events section depend on the benefit of these data to the device user. For a device cleared under Premarket Notification, which was not supported by clinical studies, the Adverse Events section might include only potential adverse events and a statement of the source of the information." It is clear to me that the suggestions in the guidance provide the manufacturer flexibility in describing adverse effects.

While there are no regulatory requirements specifying the content of patient labeling, per se,[79] manufacturers may consider industry standards and best practices when developing patient brochures or patient information.

III. History of surgical mesh products for treatment of pelvic organ prolapse, ETHICON submissions and clinical data

III.A. Pelvic Organ Prolapse (POP) Repair

The following is a description of POP and its repair by the

[76] FDA's Guidance for the Preparation of a Premarket Notification Application for a Surgical Mesh, is not a PMA requirement or a special controls document. The guidance does not include patient labeling. The need for a Special Controls document was discussed at the FDA panel meeting in 2011.

[77] Guidance on Medical Device Patient Labeling, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070782.htm.

[78] Workshop, http://www.fda.gov/medicaldevices/newsevents/workshopsconferences/ucm455361.htm#date.

[79] 21 CFR §801.109(d) is typically met for patient labeling by attachment of the IFU or reference to sources of IFU information.

Transvaginal Mesh Industry Working Group in a document presented to the FDA OB/GYN Advisory Committee meeting on September 8, 2011.[80]

> "POP is the condition that results when the normal supporting structures of the vagina deteriorate. The resultant support loss can cause any or all of the following structures to prolapse (drop out of position): urethra, bladder, bowel, and/or cervix/ uterus/ vaginal vault. This prolapse can produce such symptoms as a sensation of bulge, difficulty with bowel or bladder function, pain and/ or dyspareunia (painful intercourse). Traditional treatment options for POP include hysterectomy, colporrhaphy (plication of pubocervical or rectovaginal fascia), sacro-colpopexy (suturing of vaginal apex to the sacral promontory using either mesh or fascial bridge) performed either abdominally or laparoscopically and sacrospinous fixation (securing the vaginal apex to the sacrospinous ligament). Mesh products were introduced as supporting materials in the surgical treatment of POP to address the high levels of recurrence rates associated with traditional repairs using the patient's own tissue."

FDA's Executive Summary presented before the same FDA advisory committee meeting describes additional aspects of POP:[81]

> "The Pelvic Organ Prolapse Quantification (POP-Q) system is commonly used to describe the degree of prolapse. The most distal portion of the prolapsing tissue is measured in the anterior vagina, vaginal apex, and posterior vagina relative to the vaginal opening. The degree of prolapse is described in stages from 0 to 4 based on distance from the vaginal opening. Higher stages indicate more severe prolapse and are more likely to be symptomatic.
>
> Symptomatic POP can be managed conservatively with pelvic floor exercises or by using pessaries, or it can be repaired surgically. Surgical repair of prolapse can be performed transabdominally or transvaginally and may address one or more compartments in the vagina, depending on which areas are affected. The placement of surgical mesh is intended to increase the longevity of surgical POP repairs.
>
> Use of mesh has become common practice for abdominal repair of prolapse (e.g.,sacrocolpopexy) [**7**]. In general, sacrocolpopexy is used to support the vaginal apex and is not performed to repair prolapse that is primarily anterior or posterior. Vaginal repair of prolapse may be augmented with mesh or may be performed by tissue plication and suture only (i.e., native tissue or traditional repair).
>
> In general, mesh products for vaginal POP repair are configured to match the anatomical defect they are designed to correct. Mesh can be placed in the anterior vaginal wall to aid in the correction of cystocele (anterior repair), in the posterior vaginal wall to aid in correction of rectocele (posterior

[80] Transvaginal Industry Working Group, September 8, 2011, OB/GYN Advisory Committee Meeting, page 3.
[81] FDA Executive Summary, September 8, 2011, OB/Gyn Advisory Committee Meeting, page 12.

repair), or attached to the vaginal wall and pelvic floor ligaments to correct uterine prolapse or vaginal apical prolapse (apical repair)."

III.B. The Development of Surgical Mesh for the Treatment of POP

The FDA Executive Summary presented to the FDA OB/GYN Advisory Committee on September 8, 2011, provides a brief overview of the development of surgical mesh for the treatment of POP.[82]

> "Surgical mesh was a pre-amendments device and was classified into Class II (21 CFR 878.3300). Since the 1950s, surgical mesh has been used to repair abdominal hernias. In the 1970s, gynecologists began using surgical mesh products indicated for hernia repair for abdominal repair of POP, and in the 1990s, gynecologists began using surgical mesh for surgical treatment of SUI and vaginal repair of POP. To do so, surgeons would cut the mesh to the desired shape for SUI repair or POP repair and then place the mesh through a corresponding incision. Over time, manufacturers responded to this clinical practice by developing mesh products specifically designed for SUI and POP repair.
>
> In 1996, the Surgical Fabrics (ProteGen Sling) device manufactured by Boston Scientific Corporation became the first pre-configured surgical mesh product cleared via the 510(k) pathway for surgical treatment of SUI. (The ProteGen Sling was cleared with an indication for "pubourethral support," a phrase which implies an indication for treatment of SUI.) However, use of mesh in SUI repair, referred to as slings or tape, did not become common until after the introduction of the Tension-Free Vaginal Tape (TVT™) System, manufactured by ETHICON/GYNECARE, in 1998. This system was based on the work by Ulmsten and colleagues with the ETHICON Prolene hernia mesh. In 2002, GYNEMESH® PS, also manufactured by ETHICON/GYNECARE, became the first pre-configured surgical mesh product cleared for POP repair.
>
> Over the next few years, surgical mesh products evolved into "kits" that included tools to aid in the delivery/insertion of the mesh. The first kit for SUI repair, the Island Biosurgical Bladder Neck Suspension Kit manufactured by Island Biosurgical, Inc., was cleared in 1997. The first kits for POP repair, the AMS Apogee™ System and the AMS Perigee™ System, both manufactured by American Medical Systems, Inc., were cleared in 2004. Surgical mesh kits continue to evolve in regards to introducer instrumentation, tissue fixation anchors, surgical technique, and incorporation of absorbable materials into the mesh intended to increase material compliance.
>
> The FDA premarket notification review process did not request original clinical studies to support clearance of surgical mesh indicated for treatment of SUI or POP. Attempts to establish clinical effectiveness were undertaken later by the clinical community with clinical trials, published studies, and systematic reviews/meta-analyses. Some of this published literature was

[82] FDA Executive Summary, September 8, 2011, OB/Gyn Advisory Committee Meeting, page 5.

> incorporated into later 510(k) submissions to support market clearance.
>
> Premarket clearance of surgical mesh indicated for POP and SUI repair was typically based on pre-clinical bench and animal studies as described in the FDA Guidance Document "Guidance for the Preparation of a Premarket Notification Application for a Surgical Mesh" issued on March 2, 1999 (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073791.pdf)."
>
> "From 1992-2010, the FDA cleared 168 510(k)s for surgical mesh with urogynecologic indications."

III.C. Relevant ETHICON Regulatory Submissions to FDA

I examined records provided by counsel to help construct a history table of the ETHICON mesh submissions including GYNEMESH PS. I also did a search of the FDA 510(k) database as referenced in the table to identify additional submissions not included in the records provided by counsel.[83] I ordered the submissions by 510(k) number in the table that follows.

The records fall into three basic categories. One category is ETHICON mesh devices used for abdominal and hernia repair classified as Class II devices under 21 CFR §878.3300, Surgical Mesh. The next group falls under the same classification but has indications for use related to the repair of vaginal wall prolapse and other pelvic floor procedures. The last group again falls under the same classification regulation but includes transvaginal tapes used for stress urinary incontinence.

Since PROLENE polypropylene is a key constituent of several of the relevant ETHICON devices, its first regulatory submission is important. A predicate PROLENE polypropylene suture[84] was approved by FDA as a drug under NDA 16-374 and later the device file transitioned to the Center for Devices and Radiological Health as a premarket approval application. Later, eight types of sutures, including PROLENE sutures, were reclassified from Class III to Class II devices under 21 CFR §878.5010,[85] Nonabsorbable polypropylene surgical suture and subject to a special controls guidance document.[86] This suture is referenced as a predicate for the first vaginal tapes and meshes. Additionally, as Catherin Beath testified, "there was a pre-amendment Prolene mesh."[87]

The history continues with variations of mesh materials, and ETHICON mesh products.

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[83] Search July 2015.
[84] See ETHICON submissions table; K940498.
[85] FR Vol.68, Number 106 (Tuesday, June 3, 2003).
[86] www.accessfda.gov.
[87] Beath deposition:3/16/12;pg55:16.

K Number	Device Name	Material/Change	Predicate	Data
K962530[88] 8/9/96	PROLENE Polypropylene Mesh Nonabsorbable Synthetic Surgical Mesh	Knitted polypropylene identical to PROLENE sutures Additional sizes and key hole shape	PROLENE polypropylene mesh	Bench, preclinical
K972412 9/10/97	ETHICON PROLENE Polypropylene Mesh Hernia Device Nonabsorbable Synthetic Surgical Mesh Implant[89]	PROLENE polypropylene	BARD Marlex mesh PerFix Plug	preclinical
K974098[90] 1/28/98	Tension Free Vaginal Tape (TVT) System	Polypropylene mesh same as PROLENE mesh and PROLENE polypropylene suture	Protegen Sling[91] PROLENE Suture[92] NDA/PMA 16-374	Bench, preclinical and clinical data
K984220 2/23/1999	PROLENE (Polypropylene) Hernia System[93]	Pre-shaped	PROLENE Hernia System	No data indicated in record
K001122 5/23/2000	PROLENE Soft[94] (polypropylene) nonabsorbable Synthetic Surgical Mesh	Diameter of monofilament and pigmented strands	K962530 and Mersilene mesh (polyester fiber mesh) preamendments	Bench, K962530 preclinical, clinical based on prior Prolene mesh
K002672 11/22/2000	VYPRO Mesh[95]	Mix of polypropylene and polyglactin	PROLENE Mesh and VICRYL (polyglactin 910) Mesh	Bench
K010722 4/27/01	Polypropylene 3D Patch[96]	Three-dimensional	PROLENE Hernia system and Bard Marlex PerFix Plug	Nonclinical laboratory
K012628 10/26/01	GYNECARE[97] Tension-Free Vaginal Tape (TVT) Blue System	Addition of blue pigmented polypropylene fibers interwoven with unpigmented fibers	K974098 K001122	Bench, preclinical, K974098 clinical data
K013718 1/8/2002	GYNEMESH[98] PROLENE Soft Nonabsorbable Synthetic Surgical Mesh for Pelvic Floor Repair	Same as K001122 Pelvic floor claim	K001122 K962530 MERSILENE	K001122 for bench testing, K962530 for preclinical, published literature

[88] ETH-02240-02273.
[89] accessdata.fda.gov/cdrh_docs/pdf/K972412.pdf.
[90] 1998 submission, see Attachment.
[91] Removed from market; no effect on other products based on lack of evidence of FDA action.
[92] PROLENE mesh and suture referenced in TVT 510(k). In my experience, FDA would consider referenced marketed device information as "predicate" information, or more recently as at least "reference" device information.
[93] accessdata.fda.gov/cdrh_docs/pdf/K984220.pdf.
[94] ETH-01646-01818.
[95] accessdata.fda.gov/cdrh_docs/pdf/K002672.pdf.
[96] accessdata.fda.gov/cdrh_docs/pdf/K010722.pdf.
[97] 2001 submission, see Attachment.
[98] ETH00797-00927.

				for clinical
K031925 9/17/03	PROCEED[99] Trilaminate Surgical Mesh	Layers of PS, regular poly, ORC and polydioxanone	PROLENE soft Polypropylene Mesh	Nonclinical and in-vivo testing
K033337 4/1/2004	ULTRAPRO Mesh[100]	equal parts absorbable poliglecaprone-25 fiber and nonabsorbable polypropylene fiber	VYPRO mesh, PROLENE polypropylene mesh, MERSILENE mesh	bench and animal testing
K033568 12/8/03	GYNECARE TVT Obturator Device[101]	New accessories	K974098 K012628 K02356 (sic)	Predicate data
K042603 12/22/04	GYNECARE Prolene Fastener System	Prolene	Mitek meniscal fastener	In-vitro and in-vivo studies
K052401 11/28/05	GYNECARE TVT SECUR System[102]	Material change and needles fixed to implant; change in implantation method	K033568 K012628 K974098	Bench, Preclinical and cadaver data
K060713 5/25/06	PROCEED[103] Surgical Mesh	Change not indicated	PROCEED Trilaminate Mesh	Non indicated
K061533 12/11/06	PROCEED Ventral Patch[104]	Not clear.	PROLENE Soft PROCEED BARD Ventralex VICRYL ETHIBOND	Preclinical, bench and animal
K063562 2/26/07	GYNECARE PROSIMA Pelvic Floor Repair Systems	Precut GYNECARE GYNEMESH PS Mesh Implants and instruments; device balloon assembly; silicon	GYNECARE GYBEMESH PS Nonabsorbable PROLENE Soft Mesh Silimed Vaginal Stent	bench
K070224 4/17/07	ULTRAPRO Plug[105]	Plug and patch	ULTRAPRO mesh BARD Mesh PerFix Plug	Bench and animal
K071249 6/5/07	ULTRAPRO Hernia System[106]	Change in materials	PROLENE hernia system ULTRAPRO mesh	Bench and animal
K071512 5/15/08	GYNECARE PROLIFT Total, Anterior, and Posterior Pelvic Floor Repair Systems GYNECARE PROLIFT+M Total, Anterior, and Posterior Pelvic Floor Repair Systems[107]	PROLIFT: Same as GYNEMESH PS; precut mesh and instruments PROLIFT+M: Same as Ultrapro Mesh and PS mesh; precut mesh and instruments	PROLIFT: K013718 AMS Apogee K040537 AMS Perigee K040623 PROLIFT+M: K033337 Ultrapro Mesh K013718 K040537 AMS Apogee K040623 AMS Perogee	Bench, Cadaver, clinical
K000485	GYNECARE TVT EXACT	Introducer/needle, handle and trocar	K904098	Bench testing of new tools

[99] accessdata.fda.gov/cdrh_docs/pdf3/K031925/pdf.
[100] www.fda.gov/ohrms/dockets/ac/08/briefing.
[101] 2003 submission, see Attachment.
[102] 2005 submission, see Attachment.
[103] accessdata.fda.gov/cdrh_docs/pdf6/K060713.pdf.
[104] accessdata.fda.gov/cdrh_docs/pdf6/K061533.
[105] accessdata.fda.gov/cdrh_docs/pdf7/K070224.pdf.
[106] accessdata.fda.gov/cdrh_docs/pdf7/K071249.pdf.
[107] ETH-02015-02238, 01324-01637, 00950-01310, 01903-02014, 01318-01323.

3/16/10	Continence System[108]	change		
K082216 9/5/08	ETHICON Mesh[109]	Absorbable and nonabsorbable polymers	GYNECARE GYNEMESH PS PROLIFT+M	Functional testing
K093932 4/9/10	ETHICON Physiomesh[110]	Mesh layers, low profile	PROCEED mesh ULTRAPRO Hernia System ULTRAPRO Mesh	Bench and animal
K100485 3/16/10	GYNECARE TVT Exact Continence System[111]	accessory changes	GYNECARE TVT	Trocar tests
K100936 7/1/10	GYNECARE TVT ABBREVO[112]	Change in mesh, assembly and accessories	GYNECARE TVT-O	Bench and cadavers
K113205 6/12/12	ARTISYN Y SHAPED mesh[113]	Y shaped mesh	ALYTE mesh GYNEMESH M RESTORELLE Y	Mechanical testing
K132054 8/23/13 Special 510(k)	TVT Exact Continence System[114]	Introducer/tip change	TVT Exact K100485	bench data
K141516 10/23/14 Traditional 510(k)[115]	ETHICON Physiomesh	Macroporous mesh composed of knitted polypropylene, and polydioxanone fibers laminated to absorbable poliglecaprone	K093932 Physiomesh BARD Ventrio Patch Parietex Mesh	Bench testing per guidance, biocompatibiloty tests, animal implant test

[108] accessdata.fda.gov/cdrh_docs/pdf10/K100485.pdf.
[109] accessdata.fda.gov/cdrh_docs/pdf8/K082216.pdf.
[110] accessdata.fda.gov/cdrh_docs/pdf9/K093932.pdf.
[111] accessdata.fda.gpv/cdrh_docs/pdf10/K100485.pdf.
[112] accessdata.fda.gov/cdrh_docs/pdf10/K100936.pdf.
[113] accessdata.fda.gov/cdrh_docs/pdf/K113205.pdf.
[114] Exact, http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K132054.
[115] Physiomesh, http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K141560.

Description of GYNEMESH PS:[116]

DESCRIPTION

GYNECARE GYNEMESH™ is constructed of knitted filaments of extruded polypropylene identical in composition to PROLENE™ Polypropylene Suture, Nonabsorbable Surgical Sutures, U.S.P. (ETHICON, LLC). This material, when used as a suture, has been reported to be non-reactive and to retain its strength indefinitely in clinical use. The mesh affords excellent strength, durability, and surgical adaptability, with sufficient porosity for necessary tissue ingrowth. Blue monofilaments have been incorporated to produce contrast striping in the mesh. The mesh is constructed of reduced diameter monofilament fibers, knitted into a unique design that results in a mesh that is approximately 50 percent more flexible than standard PROLENE™ mesh.

GYNECARE GYNEMESH™ is knitted by a process which interlinks each fiber junction and which provides for elasticity in both directions. This construction permits the mesh to be cut into any desired shape or size without unraveling.

III.D. Clinical Data Supporting the Safety and Effectiveness of pelvic mesh for POP, including ETHICON GYNEMESH PS

III.D.1. Clinical data on pelvic mesh for POP discussed at FDA 2011 panel meeting

The data supporting the safety and effectiveness of pelvic mesh was discussed at the September 8, 2011 meeting of the Obstetrics and Gynecological Panel of the Medical Devices Advisory Committee. While all the data presented do not relate solely to ETHICON devices it is important to understand the overall discussions regarding this type of product.

The Transvaginal Mesh Industry Working Group provided a report, dated August 30, 2011, to the Panel and a presentation summarizing the report was given at the panel meeting. ETHICON participated in the creation of the report and presentation to the panel.

The report notes that less than 20% of the POP diagnosed population is treated surgically and less than 13% of those undergo repair with a pelvic floor repair kit. Page 10 included the randomized controlled trials to date referenced in the FDA white paper on the safety of POP.

The report states:[117]

[116] ETHICON WEB SITE 2/4/16, http://hostedvl106.quosavl.com/cgi-isapi/server.dll?8080?IFUs?.cmt1bWFyMTJAaXRzLmpuai5jb20=?GetOneDocPureFullTxt?q8io4ulaiuo4j1qt8cn6ec3nf4?8.

[117] 2011 Panel Meeting, Transvaginal Industry Working Group Docket Submission, page 10.

> "all studies cited demonstrated anatomical effectiveness of transvaginal mesh repair. Even though the difference did not reach statistical significance in two of the aforementioned studies (Carey and Iglesia), it must be noted that overall, mesh repairs showed greater anatomical success. It should also be noted, that Quality of Life (QoL) outcomes were measured using different tools in each of the studies cited above. Results reported for both mesh procedures and traditional procedures reflect statistically significant improvements in QoL scores."

Likewise, the safety of surgical mesh was evaluated, and on pages 11-14 conclusions from studies indicated that different treatment options had similar complication rates, although the surgical options had their own inherent risks that differ in number and severity. The most appropriate surgical option should be based on the type of prolapse, general physical condition and history of the patient, as well as the surgeon's specific expertise. The report states:[118]

> "mesh exposure is the most commonly reported AE for mesh kits. Mesh exposure through the vaginal epithelium is a well characterized adverse event that can be successfully managed in the majority of cases."

> "Dyspareunia and pelvic pain following POP repair, with or without mesh, are often due to a number of causes such as pre-existent pelvic pain, estrogen deficiency and vaginal foreshortening. Both are highly complex to evaluate and currently there is limited robust data. Pelvic organ prolapse repair, whether abdominal or vaginal, whether using native tissue or mesh, appears to have a high rate of associated dyspareunia. Transvaginal mesh repairs have de novo dyspareunia rates comparable to traditional repairs."

> "…[M]esh shrinkage is a well recognized complication, as previously studied in abdominal hernia surgery."

The FDA Executive Summary provided to the Panel for the meeting also discusses the available data. FDA states:[119]

> "among the 60 articles reviewed on the treatment of POP using surgical mesh, 22 were randomized controlled trials (RCTs), and 38 were observational studies. Additionally, 15 systematic or meta-analysis were reviewed. For these 60 articles, the number of treatment groups or cohorts ranged from 1 to 3, and the number of patients per treatment group or cohort ranged from 13 to 577. The majority of the studies evaluated anterior prolapse repair, followed by posterior and apical vaginal repair. The duration of follow-up ranged from perioperative (intraoperative to 48 hours post-operative) to 60 months…the majority of the studies reported adverse events and outcomes of perioperative period to 12 months postoperative. Only five studies reported a follow-up period beyond 12 months."

The FDA review identified a number of limitations with the existing

[118] Ibid., page 13.
[119] FDA Executive Summary, September 8, 2011, OB/Gyn Advisory Committee Meeting, page 16.

literature:[120]

> "(1) results reflect both primary and repeat prolapse repairs, (2) most studies involve concomitant surgical procedures, (3) adverse event reporting is inconsistent, (4) inclusion/exclusion criteria are incompletely documented, (5) the majority of RCTs are not evaluator-blinded or adequately powered, and (6) few studies extend beyond two years.
>
> In addition, the literature on POP repair largely represents studies in which the primary endpoint was ideal anatomic support, defined as prolapse Stage 0 or 1 (i.e., the lowest point of prolapse is more than 1 cm proximal to the vaginal opening). This outcome is not based on a correlation with symptomatology and is not necessary for most women to achieve symptomatic relief."

FDA's summary also discussed mesh erosions and the other sequelae also presented by the Industry Working Group. FDA noted that the level of surgeon experience in pelvic floor reconstructive surgery and training in POP mesh procedures might affect the development of mesh complications, but not exclusively.

[120] FDA Executive Summary, September 8, 2011, OB/Gyn Advisory Committee Meeting, page 17.

Table 5-1: Randomized Controlled Trials Comparing Mesh Repair to Native Vaginal Tissue Repair

LEVEL 1 RCT Study	Year	# Patients	Follow Up	Anatomic Cure Mesh	Anatomic Cure Traditional	p
Sivaslioglu[14]	2008	90	12	91% Ant	72%	p<.05
Nguyen[15]	2008	75	12	87% Ant	55%	p<.05
Carey [16]	2009	139	12	81% Ant/Post	65.6%	p=.07
Nieminen[17]	2010	202	36	87% Ant	59%	p<.0001
Iglesia[18]	2010	65	9.7	40.6 All	29.6	NS
Withagen[10]	2011	194	12	90.4 All	54.8	p<.001
Altman[11]	2011	389	12	82.3 Ant	47.5	p=0.008

III.D.2. GYNEMESH PS Clinical Information

The predicates for GYNEMESH PS are PROLENE soft mesh, PROLENE mesh and MERSILINE mesh.[121] The original 510(k) for GYNEMESH PS ETHICON included references to several published reports on PROLENE and MERSILENE mesh as follows:[122]

[121] ETH-00844.
[122] ETH-0084-00848.

Cundiff GW, Harris RL, Coates K, Low VH, Bump RC, Addison WA.
Abdominal sacral colpoperineopexy: a new approach for correction of posterior compartment defects and perineal descent associated With vaginal vault prolapse.
Am J Obstet Gynecol. 1997 Dec;177(6):1345-53; discussion 1353-5.

Diana M, Zoppe C, Mastrangeli B.
Treatment of vaginal vault prolapse with abdominal sacral colpopexy using prolene mesh.
Am J Surg. 2000 Feb;179(2):126-8

Julian TM.
The efficacy of Marlex mesh in the repair of severe, recurrent vaginal prolapse of the anterior midvaginal wall.
Am J Obstet Gynecol. 1996 Dec,175(6):1472-5.

Kohli N, Walsh PM, Roat TW, Karram MM.
Mesh erosion after abdominal sacrocolpopexy.
Obstet Gynecol. 1998 Dec;92(6) 999-1004.

Migliari R, De Angelis M, Madeddu G, Verdacchi T.
Tension-free vaginal mesh repair for anterior vaginal wall prolapse.
Eur Urol. 2000 Aug;38(2):151-5.

Nicita G.
A new operation for genitourinary prolapse.
J Urol. 1998 Sep;160(3 Pt 1):741-5.

Visco AG, Weidner AC, Barber MD, Myers ER, Cundiff GW, Bump RC, Addison WA.
Vaginal mesh erosion after abdominal sacral colpopexy.
Am J Obstet Gynecol. 2001 Feb;184(3):297-302.

Winters JC, Cespedes RD, Vanlangendonck R.
Abdominal sacral colpopexy and abdominal enterocele repair in the management of vaginal vault prolapse.
Urology. 2000 Dec 4;56(6 Suppl 1):55-63.

The Clinical Expert Reports by ETHICON medical directors describe in detail supporting clinical data from the date of the initial marketing of GYNEMESH PS through 2013.[123]

IV. FDA Communications Regarding the Treatment of Pelvic Organ Prolapse

IV.A. FDA Public Health Notification, October 20, 2008.

FDA issued a Public Health Notification (PHN) on Surgical Mesh, following its examination of adverse events related to various surgical meshes sold by numerous different manufacturers.[124]

The PHN states:

> "This is to alert you to complications associated with transvaginal placement of surgical mesh to treat Pelvic Organ

[123] ETH.MESH.10179518-10179636, 00082250-00082273, 03715787-03715793.

[124] http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/ucm061976.htm.

Prolapse (POP) and Stress Urinary Incontinence (SUI). Although rare (emphasis added), these complications can have serious consequences. Following is information regarding the adverse events that have been reported to the FDA and recommendations to reduce the risks.

Nature of the Problem

Over the past three years, FDA has received over 1,000 reports from nine surgical mesh manufacturers of complications that were associated with surgical mesh devices used to repair POP and SUI. These mesh devices are usually placed transvaginally, utilizing tools for minimally invasive placement.

The most frequent complications included erosion through vaginal epithelium, infection, pain, urinary problems, and recurrence of prolapse and/or incontinence. There were also reports of bowel, bladder, and blood vessel perforation during insertion. In some cases, vaginal scarring and mesh erosion led to a significant decrease in patient quality of life due to discomfort and pain, including dyspareunia.

Treatment of the various types of complications included additional surgical procedures (some of them to remove the mesh), IV therapy, blood transfusions, and drainage of hematomas or abscesses.

Specific characteristics of patients at increased risk for complications have not been determined. Contributing factors may include the overall health of the patient, the mesh material, the size and shape of the mesh, the surgical technique used, concomitant procedures undertaken (e.g. hysterectomy), and possibly estrogen status.

Recommendations

Physicians should:

- Obtain specialized training for each mesh placement technique, and be aware of its risks.
- Be vigilant for potential adverse events from the mesh, especially erosion and infection.
- Watch for complications associated with the tools used in transvaginal placement, especially bowel, bladder and blood vessel perforations.
- Inform patients that implantation of surgical mesh is permanent, and that some complications associated with the implanted mesh may require additional surgery that may or may not correct the complication.
- Inform patients about the potential for serious complications and their effect on quality of life, including pain during sexual intercourse, scarring, and narrowing of the vaginal wall (in POP repair).
- Provide patients with a written copy of the patient labeling from the surgical mesh manufacturer, if available."

FDA often provides industry a draft of its public health notice and solicits comments before FDA finalizes the document. Although FDA may

consider comments, Catherine Beath correctly noted in her testimony "FDA ultimately owns the final version."[125]

IV.B. FDA Safety Communication, July 13, 2011.

On July 13, 2011, FDA issued an updated safety notice concerning serious complications associated with transvaginal placement of surgical mesh for pelvic organ prolapse.[126] Like the 2008 PHN, this update was not specific to ETHICON's products, but rather addressed the entire class of surgical meshes used to treat POP.

The PHN states, in part:

> "The FDA is issuing this update to inform you that serious complications associated with surgical mesh for transvaginal repair of POP are **not rare**. This is a change from what the FDA previously reported on Oct. 20, 2008. Furthermore, it is not clear that transvaginal POP repair with mesh is more effective than traditional non-mesh repair in all patients with POP and it may expose patients to greater risk. This Safety Communication provides updated recommendations for health care providers and patients and updates the FDA's activities involving surgical mesh for the transvaginal repair of POP.
>
> From 2008 – 2010, the most frequent complications reported to the FDA for surgical mesh devices for POP repair include mesh erosion through the vagina (also called exposure, extrusion or protrusion), pain, infection, bleeding, pain during sexual intercourse (dyspareunia), organ perforation, and urinary problems. There were also reports of recurrent prolapse, neuro-muscular problems, vaginal scarring/shrinkage, and emotional problems. Many of these complications require additional intervention, including medical or surgical treatment and hospitalization.
>
> In order to better understand the use of surgical mesh for POP and SUI, the FDA conducted a systematic review of the published scientific literature from 1996 – 2011 to evaluate its safety and effectiveness. The review showed that transvaginal POP repair with mesh does not improve symptomatic results or quality of life over traditional non-mesh repair. The FDA continues to evaluate the literature for SUI surgeries using surgical mesh and will report about that usage at a later date.
>
> In particular, the literature review revealed that:
> - Mesh used in transvaginal POP repair introduces risks not present in traditional non-mesh surgery for POP repair.
> - Mesh placed abdominally for POP repair appears to result in lower rates of mesh complications compared to transvaginal POP surgery with mesh.

[125] Beath deposition:3/6/12, page 261:24-25.
[126] http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm262435.htm.

- There is no evidence that transvaginal repair to support the top of the vagina (apical repair) or the back wall of the vagina (posterior repair) with mesh provides any added benefit compared to traditional surgery without mesh.
- While transvaginal surgical repair to correct weakened tissue between the bladder and vagina (anterior repair) with mesh augmentation may provide an anatomic benefit compared to traditional POP repair without mesh, this anatomic benefit may not result in better symptomatic results.

The FDA's literature review found that *erosion* of mesh through the vagina is the *most common and consistently reported mesh-related complication* from transvaginal POP surgeries using mesh. Mesh erosion can require multiple surgeries to repair and can be debilitating for some women. In some cases, even multiple surgeries will not resolve the complication.

Mesh contraction (shrinkage) is a *previously unidentified risk* of transvaginal POP repair with mesh that has been reported in the published scientific literature and in adverse event reports to the FDA since the Oct. 20, 2008 *FDA Public Health Notification*. Reports in the literature associate mesh contraction with vaginal shortening, vaginal tightening and vaginal pain.

Both mesh erosion and mesh contraction may lead to severe pelvic pain, painful sexual intercourse or an inability to engage in sexual intercourse. Also, men may experience irritation and pain to the penis during sexual intercourse when the mesh is exposed in mesh erosion. The complications associated with the use of surgical mesh for POP repair have not been linked to a single brand of mesh."

The notice restated the October 20, 2008, physician recommendations and added the following:

- "Recognize that in most cases, POP can be treated successfully without mesh thus avoiding the risk of mesh-related complications.
- Choose mesh surgery only after weighing the risks and benefits of surgery with mesh versus all surgical and non-surgical alternatives.
- Consider these factors before placing surgical mesh:
  - Surgical mesh is a permanent implant that may make future surgical repair more challenging.
  - A mesh procedure may put the patient at risk for requiring additional surgery or for the development of new complications.
  - Removal of mesh due to mesh complications may involve multiple surgeries and significantly impair the patient's quality of life. Complete removal of mesh may not be possible and may not result in complete resolution of complications, including pain.
  - Mesh placed abdominally for POP repair may result in lower rates of mesh complications compared to transvaginal POP surgery with mesh.
- Inform the patient about the benefits and risks of non-surgical options, non-mesh surgery, surgical mesh placed abdominally and

the likely success of these alternatives compared to transvaginal surgery with mesh.
- Notify the patient if mesh will be used in her POP surgery and provide the patient with information about the specific product used.
- Ensure that the patient understands the postoperative risks and complications of mesh surgery as well as limited long-term outcomes data."

The PHN also added instructions for patients as follows:

"Before Surgery

Be aware of the risks associated with surgical mesh for transvaginal repair of POP. Know that having a mesh surgery may put you at risk for needing additional surgery due to mesh-related complications. In a small number of patients, repeat surgery may not resolve complications.
Ask your surgeon about all POP treatment options, including surgical repair with or without mesh and non-surgical options, and understand why your surgeon may be recommending treatment of POP with mesh.

In addition, ask your surgeon these questions before you agree to have surgery in which surgical mesh will be used:
- Are you planning to use mesh in my surgery?
- Why do you think I am a good candidate for surgical mesh?
- Why is surgical mesh being chosen for my repair?
- What are the alternatives to transvaginal surgical mesh repair for POP, including non-surgical options?
- What are the pros and cons of using surgical mesh in my particular case? How likely is it that my repair could be successfully performed without using surgical mesh?
- Will my partner be able to feel the surgical mesh during sexual intercourse? What if the surgical mesh erodes through my vaginal wall?
- If surgical mesh is to be used, how often have you implanted this particular product? What results have your other patients had with this product?
- What can I expect to feel after surgery and for how long?
- Which specific side effects should I report to you after the surgery?
- What if the mesh surgery doesn't correct my problem?
- If I develop a complication, will you treat it or will I be referred to a specialist experienced with surgical mesh complications?
- If I have a complication related to the surgical mesh, how likely is it that the surgical mesh could be removed and what could be the consequences?
- If a surgical mesh is to be used, is there patient information that comes with the product, and can I have a copy?

After Surgery
- Continue with your annual and other routine check-ups and follow-up care. There is no need to take additional action if you are satisfied with your surgery and are not having complications or symptoms.

- Notify your health care provider if you have complications or symptoms, including persistent vaginal bleeding or discharge, pelvic or groin pain or pain with sex, that last after your follow-up appointment.
- Let your health care provider know you have surgical mesh, especially if you plan to have another surgery or other medical procedures.
- Talk to your health care provider about any questions you may have.

If you had POP surgery, but do not know whether your surgeon used mesh, ask your health care provider at your next scheduled visit."

IV.C. FDA 2011 Panel Meeting

As noted above, on September 8-9, 2011, FDA convened a meeting of the Obstetrics and Gynecology Devices Panel of the Medical Devices Advisory Committee to discuss the safety and effectiveness of surgical mesh for the treatment of stress urinary incontinence and transvaginal surgical mesh for the repair of pelvic organ prolapse. FDA asked the Panel specific questions and the Panel responded as follows:[127]

1a. Is the list of complications read to the Panel complete? The answer was a general yes but that a preponderance of the group felt that they required more evidence to actually answer those questions.

1b. What is the Panel's views on effectiveness of mesh for POP? The answers were mixed whether the benefits outweighed the risks.

2a. Are clinical studies needed for premarket evaluation? The answer was yes and should involve some sort of control group.

2b. Are special controls needed and what type? The answer was yes and types were registries and guidelines.

2c. Should the devices be reclassified to Class III? There were mixed responses.

3. Are 522 studies needed? The general answer was yes.

4. Is abdominal placement of mesh for POP well-established and are clinical data or 522 studies needed? The answer was yes and the Panel provided some opinions on study parameters.

IV.D. FDA Section 522 Orders

On January 3, 2012, FDA issued Section 522 postmarket study orders to various mesh manufacturers, including five orders to ETHICON for GYNEMESH PS, PROLIFT, PROLIFT+M, Prosima and TVT Secur.[128] The orders

[127] Panel transcript, Free State Reporting, Inc.
[128] 522 study listing, http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pss.cfm?start_search=E#E.

stipulated the conduct of postmarket surveillance studies for each device subject to an order and safety and effectiveness questions to be answered from the data to be collected in the studies.[129] Notably, FDA had not required postmarket studies when it cleared GYNEMESH PS in 2002.

On February 1, 2012, ETHICON responded to FDA's 522 order for GYNEMESH PS (PS120046).[130] ETHICON proposed that the 522 study plan for PROSIMA suffice for GYNEMESH PS since the intended use of both products was the same. In April 2012 FDA requested additional information on the plan.[131]

IV.E. ETHICON Proposes a Change in GYNEMESH PS Labeling and the 522 order is suspended

On May 9, 2012, ETHICON requested FDA to consider a change in GYNEMESH PS labeling to narrow the indication for use to sacrocolpopexy procedures only.[132]

On June 5, 2012, ETHICON notified surgeons by letter that it was discontinuing marketing of its pelvic floor repair systems (e.g., PROLIFT, PROLIFT+M and PROSIMA) after carefully considering numerous factors.[133] The notice states “On a global basis, these factors include the commercial viability of these products in competitive and declining worldwide markets, the complexities of the regulatory environments in which we operate, and the availability of other treatment options for these pelvic conditions.” In an August 3, 2012, letter to Dr. med. Kurt Lobodasch[134] the FDA states “Johnson and Johnson has decided to terminate their product line of surgical mesh intended for transvaginal pelvic floor procedures, however, the FDA has not issued a withdrawal letter or directed any company to discontinue the distribution of their products based on the 2011 Panel recommendations, or on its own accord.”

The notice also states "In addition to the discontinuation of these products we plan to pursue an Indication for use change on GYNEMESH PS, indicating it for abdominal (open or laparoscopic) use only."

FDA agreed with ETHICON's request to narrow GYNEMESH PS labeling and also suspended the 522 study order, provided ETHICON meet certain stipulations.[135] On November 5, 2012, ETHICON provided the FDA-stipulated information including a revised IFU, 510(k) Summary, and Indications for Use form.[136] FDA acknowledged the information with a revised 510(k) clearance order on November 7, 2012.

[129] ETH.MESH.030467737-030467740.
[130]
[131] ETH.MESH.04474779.
[132] ETH.MESH.04474315-04474316.
[133] ETH.MESH.04568045.
[134] See Attachment.
[135] ETH.MESH.04927342-04927343.
[136] ETH.MESH.

The April 2013 Clinical Expert Report by Dr. Hinoul describes the change as follows:[137]

> The application of the device is fully described in the Instructions for Use (IFU), which has recently been revised to reflect a new Indication for Use that allows for transabdominal mesh placement only. The original indications for use allowed for mesh placement transvaginally or abdominally. The revised indication for abdominal placement was implemented as a result of Ethicon's commercial decision in June 2012 to discontinue the sale of transvaginal mesh products for pelvic floor disorders. This decision was not based on product safety or effectiveness. GYNEMESH™ PS is one of the most studied meshes on the market and has been safely and effectively used for treatment of pelvic floor disorders. In addition, the
>
> Contraindications, Warnings/Precautions and Adverse Reactions sections of the IFU were revised to be aligned with labelling associated with a recently approved mesh product that is used in a similar manner (Artisyn Y Mesh).
>
> GYNECARE GYNEMESH™ PS is indicated for use as a bridging material for apical vaginal and uterine prolapse where surgical treatment (laparotomy or laparoscopic approach) is warranted.

IV.F. FDA Reclassification of Surgical Mesh for POP and Call for PMAs

On January 5, 2016, the Food and Drug Administration issued a final order reclassifying surgical mesh for transvaginal pelvic organ prolapse (POP) repair from class II to class III and established a date requiring premarket approval for these devices.[138] FDA reclassified this type of device to Class III based on the criteria for Class III devices, which is an FDA determination that general controls and special controls together are not sufficient to provide reasonable assurance of safety and effectiveness for this type of device, and these devices present a potential unreasonable risk of illness or injury. The reclassification orders do not apply to Gynemesh PS as it is indicated for abdominal, as opposed to transvaginal, placement.

FDA received comments on the proposal to reclassify surgical mesh for POP repair. In the reply to comment 3 FDA stated it does not believe that a ban, recall or suspension of use of surgical mesh for transvaginal POP repair is warranted at this time. FDA also stated it believes "there are potential benefits from surgical mesh used for transvaginal POP repair including treatment of POP in appropriately selected women with severe or recurrent prolapse. As such, FDA has not determined that this device presents an unreasonable and substantial risk of illness or injury" and "there is not sufficient evidence at this time to support a finding that there is a reasonable probability that surgical mesh for transvaginal repair of POP would cause serious adverse health consequences or death."

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[137] ETH.MESH.10179522-10179523.
[138] 81 FR 353 and 81 FR 363.

VIII. Opinions

In forming my opinions, I employed methodologies consistently used by health care companies and regulatory authorities to address and evaluate premarket, quality system, post-approval and labeling data and information. These methods are also consistent with those utilized by me, the sole member of Ulatowski Consulting, LLC, in the conduct of my assignments with both U.S. and international health care clients manufacturing medical devices including preparation of regulatory submissions and post-market efforts, preparation of regulatory and scientific protocols, labeling and other medical device evaluations. My opinions are also predicated upon the Food, Drug, and Cosmetic Act, the Code of Federal Regulations, Federal Registers, guidance and device standards, and industry practices and standards.

My participation in this litigation and the development of the opinions enclosed herein follow an extensive review process. As described earlier, I possess extensive experience in the medical device industry and draw on this experience in conducting my tasks under the auspices of Ulatowski Consulting, LLC, including the reviews provided herein.

As described, I have performed a thorough and integrated review of the publicly available information and regulatory documents, including those produced during discovery, identified in this report and listed in Exhibit B. I analyzed those documents for their relevance. The employed methodology also included a review of the production documents, depositions/transcripts, and other materials provided to me by Counsel, or requested by me from Counsel. Upon retrieval, receipt, and review I considered documents for possible inclusion in the evaluation for this report. If additional relevant proprietary documentation was required, and I was unable to independently locate this data/information, I made a request of Counsel for any related documents to be reviewed by me. I analyzed these documents for their regulatory relevance and conformity to industry practices and standards in forming my opinions in the same manner I would have assessed them when I was a premarket evaluator or the chief medical device compliance officer at FDA, and also in the same way I would evaluate them in my current capacity as a consultant to companies on medical device regulatory aspects.

The employed methods also include my reviews of depositions, corresponding exhibits, potentially associated with regulatory affairs, post-market surveillance, device design and manufacturing, among others. Reviews of depositions and exhibits are critical. Because I have been engaged in all the aspects of medical device design, development and commercialization, I can interpret and evaluate industry testimony.

Based upon my analysis of these documents and information, as well as my experience, knowledge, and training, I have formed opinions with regard to GYNEMESH PS. Each of the opinions set forth below is held to a reasonable degree of scientific and regulatory certainty. My prior testimony is listed in Exhibit C. I have no publications in the past 10 years.

I may use visual aids or demonstrative exhibits, such as diagrams, images, slides or charts, to illustrate and or explain my opinions and

analyses in this report, as well as excerpts, charts, and other information from the materials I have cited in my report or identified in the materials reviewed.

I reserve the right to supplement this report and my opinions as discovery progresses in this case.

Opinion 1. It is my opinion the GYNEMESH PS 510(k) establishes that it is as safe and effective as predicate surgical meshes, and therefore there was reasonable assurance that the device was safe and effective.

ETHICON submitted a 510(k) for GYNEMESH PS on November 6, 2001.[139] FDA cleared the 510(k) for GYNEMESH PS on January 8, 2002. ETHICON relied on the FDA guidance entitled "Guidance for the preparation of a premarket notification application for a surgical mesh" for the content and format of the submission. The indication for use was as follows:

> GYNEMESH PROLENE Soft (Polypropylene) Mesh is indicated for tissue reinforcement and long-lasting stabilization of fascial structures of the pelvic floor in vaginal wall prolapse where surgical where surgical treatment is intended, either as mechanical support or bridging material for the fascial defect.

ETHICON made it clear in the 510(k) that GYNEMESH PS was the same as PROLENE Soft mesh but with a change in indication as follows:

> GYNEMESH PROLENE Soft (Polypropylene) Mesh for Pelvic Floor Repair, herein referred to as GYNEMESH PROLENE Soft Mesh, is identical in material and composition to existing devices: PROLENE Soft (Polypropylene) Mesh K001122 cleared May 23, 2000, PROLENE (Polypropylene) Mesh K962530 cleared by FDA on August 9, 1996. GYNEMESH PROLENE Soft Mesh is also substantially equivalent to MERSILENE Mesh in functionality. MERSILENE Mesh is a preamendment medical device.
>
> This Premarket Notification is submitted to modify the indication to be used as a reinforcement of fascial structures of the pelvic floor in the vaginal wall prolapse when surgical treatment is intended either as mechanical support or bridging material for the fascial defect.

ETHICON informed FDA that the material of GYNEMESH PS is constructed of polypropylene fibers approved by FDA in the PROLENE suture NDA/PMA 16-374. ETHICON also referenced the additional products Surgical Fabrics and SURGISIS which had similar intended uses. ETHICON documented as with PROLENE Soft mesh the technological characteristics of burst, tear and tensile strength, suture pull out and flexibility were less than PROLENE mesh but more than MERSILENE mesh. GYNEMESH PS and PROLENE Soft

[139] ETH-00807-00927.

mesh is thinner than PROLENE mesh with a different knit pattern and smaller diameter fibers. The test data for PROLENE Soft mesh applied to GYNEMESH PS and was detailed in the 510(k).

For clinical data ETHICON provided tabular information on prior relevant clinical literature summarized as follows:

> Polypropylene sutures, polypropylene mesh and the predicate devices, PROLENE Soft Mesh, PROLENE Mesh and MERSILENE Mesh, have an established history of safe clinical use as implantable materials.
>
> To support the use of GYNEMESH PROLENE Soft Mesh as a reinforcing or bridging material in fascial deficiencies in the pelvic floor, the following is a summary of the published literature on the use of PROLENE Mesh and MERSILENE Mesh materials in Pelvic Floor Repairs. The actual published reports are in attachment Appendix VI.

I evaluated the 510(k) as I did while a premarket reviewer for over 25 years relying on the standard for a determination of substantial equivalence in FDA guidance. The intended use of GYNEMESH PS was the same as the predicates identified in the submission although the indicated use was specifically for use in the pelvis. The technological characteristics of GYNEMESH PS were the same as PROLENE Soft mesh. Given that the only difference between GYNEMESH PS and PROLENE Soft mesh was the indication for use the engineering and clinical information on the predicate was applicable to GYNEMESH PS. I find that GYNEMESH PS was equivalent to the predicates.

In finding GYNEMESH PS equivalent to the predicates I am concluding that it is as safe and effective as the predicates. The Act provides that the controls applicable to its class provide reasonable assurance of safety and effectiveness of the devices in the class. The clearance of GYNEMESH PS by the 510(k) route was the existing premarket control when FDA cleared it.

Opinion 2. In my opinion, GYNEMESH PS Instructions for Use (IFUs) were substantially compliant with prescription device regulatory requirements and industry standards and practices. As such, the IFUs were not misbranded. Additionally, ETHICON medical staff applied a reasonable process to specify the risks and warnings in the IFUs.

As noted below, ETHICON medical staff did not believe that certain contraindications, or adverse effects were warranted in the IFUs. It is evident to me from a regulatory perspective that the ETHICON medical staff applied a reasonable medically-based process to determine what risks and warnings to specify in the IFUs. In addition, FDA considers common knowledge and training of doctors in disease conditions and treatments when evaluating IFUs. The IFUs are not intended to be medical textbooks.

Dr. Charlotte Owens, medical director at ETHICON at the time of the

launch of PROLIFT, a mesh for repair of prolapse, testified regarding the contents of a mesh for repair of pelvic organ prolapse, which are applicable as well to the GYNEMESH PS IFU:

> "Surgeons don't have to figure out the complications of an area that they operate. Surgeons are trained to know the complications of the area in which they operate."[140]
>
> "We listed adverse reactions that we knew were adequate and sufficient for this document."[141]
>
> "Pain is a commonly known risk of pelvic floor repair in all surgeries."[142]

Dr. Aaron Kirkemo, a medical director at ETHICON, testimony is also applicable to GYNEMESH PS. He stated as follows:

> Question: "And I want to ask you to tell me if you see information indicating there's a "potential for serious complications and their effect on the quality of life, including pain during sexual intercourse scarring and narrowing of the vaginal wall"
>
> Answer: "In the IFU…it talks about all of the conditions that can lead to these sort of problems."[143]

Dr. David Robinson, a medical director at ETHICON, also provided testimony applicable to GYNEMESH PS as follows:

> "It would be obvious to a pelvic floor surgeon or, in fact, virtually any surgeon that injury to nerve can cause pain."[144]
>
> "I think they would have, absolutely have the knowledge, whether it's mesh or scar tissue related to mesh, contracture could cause pain."[145]
>
> "Data from TVM simply did not support putting those (chronic pain and dyspareunia) in (the IFU)."[146]

Dr. Piet Hinoul, a medical director at ETHICON, testified:

> "…bringing the vagina back into the inside allows many of them to return to have a healthy sex life. Any procedure you do to restore that, any procedure you do on the vagina may result in painful intercourse…It is the same for PROLIFT as it is for a Richter sacrospinous ligament fixation or even a sacrocolpopexy."[147]

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[140] Owens deposition:9/12/12 pg.262;21-25.
[141] Owens deposition:9/12/12 pg.310;10-13.
[142] Owens deposition:9/13/12 pg.553;18-20.
[143] Kirkemo deposition:4/18/12;pages 231:19-23.
[144] Robinson deposition:8/23/12;pages 966:5-7.
[145] Robinson deposition:3/14/12;pages 456:21-24.
[146] Robinson deposition:3/13/12;pages 309:13-15.
[147] Hinoul deposition:9/19/12;pages 303:15-24.

> "…for anybody that has ever done this kind of surgery or even heard about this kind of surgery, knows that this could lead to dyspareunia or pain…any procedure that deals with pelvic floor repair may cause dyspareunia."

The IFU for GYNEMESH PS as submitted to FDA in 2001 included sections on all the information required by the FDA labeling regulation, 21 CFR Part 801 for prescription devices.[148] The labeling was consistent with the predicate labeling contents. The sections in the IFU include a description of the device, indication for use, contraindications, precautions, warnings, adverse effects and other prescribing information.

The IFU submitted to FDA in 2012, when ETHICON proposed to narrow the indications for use exhibited expanded information to reflect the evolution of knowledge regarding warnings, precautions and adverse effects for mesh devices and the current thinking of FDA on IFU information.

Opinion 3. It is my opinion that ETHICON's complaint and medical device reporting procedures and documentation were substantially compliant with regulations, industry standards and practices. ETHICON's mandatory reporting decisions were substantially compliant with regulations, industry standards and practices.

Processes and Procedures

I evaluated ETHICON complaint and reporting processes and procedures in effect before, during and after the Plaintiff's surgery to determine the extent of their compliance with relevant FDA regulations and consistency with industry practices and standards.

Franchise Policy for Product Complaint Management, PL0000087 undated[149], states, "it outlines the required elements for all complaints relating to ETHICON franchise products to ensure compliance to J&J policy, regulatory requirements, and voluntary standards." It is a high level document and describes the general regulatory elements for complaint and MDR processes. It does not address CAPA except in terms of escalation to CAPA. It is the first revision of the policy[150] put in place in 2010.

A version of the Franchise Complaint Procedure, PR-0000118, version 18,[151] put in effect in 2011 provides details on elements of the complaint process described in the above policy. Some of the key elements include certain definitions such as adverse event and incident, minimum information required in a complaint file, complaint investigation, design history review, medical review, serious injuries, deaths and/or incidents. In regard to medical review the procedure states for 5.2.8."(Medical) Review may be requested to help in determination of device relationship to reported event, to

[148] ETH-00827-00833.
[149] ETH.MESH.03743182-03743193.
[150] Lamont deposition:4/5/12;pages 485:4-7.
[151] ETH.MESH.03743365-03743387.

determination of severity of an event for purposes of adverse event reporting."[152] Section 5.2.11.4 states "Medical Assessment: For the reported event, the WCQ Medical Director will write a medical assessment based on the reported complaint information and include one of the following conclusions in the investigation comments (refer to Appendix V for definitions):

- The Device Caused Event
- The Device Contributed to Event
- The Device Potentially Contributed to Event
- The Device Not Likely Related to Event
- The Device is Not Related to Event
- Not Enough Information to Draw a Conclusion

If the Medical Assessment concludes that the device Caused, Contributed to or Potentially Contributed to the Event, then the medical assessment should also include commentary on whether or not the resultant harm is an anticipated outcome of the device or that the outcome is noted in the labeling."

The Franchise Procedure for Summary and Individual Medical Device Reporting, PR551-06, revision 30,[153] provides the detailed procedures for MDR decision-making. It includes summary decision trees including the elements of death and serious injury and malfunction related aspects, and whether the event may be related to the device. It includes consideration whether there is information or medical rationale that states the device did not cause or contribute to a death. It includes aspects not only required by the MDR regulation but also company specified steps such as treatment of litigation files, sutures, and packaging.

ETHICON has postmarket procedures.[154] ETHICON created postmarket surveillance reports assessing MDRs, complaints, CAPAs and other information.[155] One element of postmarket surveillance is the monitoring of clinical information such as published studies.

Dr. Hinoul testified, "we believe very strongly in postmarket surveillance and postmarket follow-up of our products"[156]

FDA Correspondence Regarding Procedures

I evaluated a series of correspondences regarding an FDA Form 483 observation[157] dated 9/8/05 for an ETHICON Parsippany, NY facility.[158] The FDA observation states, "Investigation of MDR reportable complaints did not include a determination whether the device failed to meet its performance specifications." ETHICON responded to the Form 483

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[152] Lamont testifies that this was in place since 2006, Lamont deposition:4/5/12;page 492:8.
[153] ETH.MESH.03589458-03589480.
[154] Lamont deposition:4/14/12;page 215:15-17.
[155] ETH.MESH.00311734-00311760.
[156] Hinoul deposition:9/19/12;pages 296:20-22 and 297:4-7.
[157] "The FDA Form 483 does not constitute a final Agency determination of whether any condition is in violation of the FD&C Act or any of its relevant regulations. (http://www.fda.gov/ICECI/EnforcementActions/ucm256377.htm).
[158] ETH.MESH.00319683.

observation on 10/5/05, 12/15/05 and 3/14/06.[159] ETHICON responded to FDA that its current procedures addressed product evaluation, device history record review, medical review and due diligence to obtain information, and when to open a CAPA. ETHICON stated that there were areas for process and documentation improvement and implemented those changes. I believe these activities were consistent with a prudent manufacturer's efforts to continuously improve its procedures.

Opinion 4. It is my opinion that ETHICON's risk management policies, processes and procedures related to GYNEMESH PS were substantially compliant with regulations, FDA guidance, industry practices and standards.

I evaluated quality management system documents to determine if they provide evidence of a substantially compliant quality and risk management systems. There is no requirement for a risk management system in 21 CFR Part 820[160] but many manufacturers, like ETHICON, have such a life-cycle system in place to additionally help ensure the safety and effectiveness of their devices. Devices marketed in Europe must have a risk management system and European Union auditors monitoring conformity of the quality and risk management systems to the Medical Device Directives will audit the risk management systems.

I assessed the following procedures to determine their conformity to the quality system regulation:

- Internal Audit Report.[161]

  Internal audits are a requirement of the quality system regulation. FDA does not review these audits or CAPAs derived from these audits during FDA inspections to encourage continuous improvement by manufacturers.

- Work Instructions for Device Design Risk Management.[162]

  These instructions provide the specific steps and flow for DMEA and DDSA creation and approval.

- Risk Management Plan, ETHICON Inc. Legacy Devices, 5/30/08.[163]

  This 5 page document from 2008 details the steps for evaluation of risk for the specified legacy devices.

- Company Procedure for Medical Device Risk Management Plan.[164]

  This is similar to the above plans that track with ISO 14971:2007.

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[159] ETH.MESH.00330769-00330775, ETH.MESH.00319665-00319672, ETH.MESH.04095019-04095026.
[160] 21 CFR Part 820 requires only a risk analysis; ISO 14971 standard describes the elements of a risk management system.
[161] ETH.MESH.02252263-02252277.
[162] ETH.MESH.03742546-03742570.
[163] ETH.MESH.02311368-02311372.
[164] ETH.MESH.00070187-00070211.

- Franchise Procedure for the Control and Disposition of Nonconforming Product and Nonconformance Processing.[165]

This procedure deals with the identification, documenting, segregating, evaluating, control and disposition of product that does not meet a specified requirement.

- Franchise Procedure for Corrective and Preventive Action (CAPA).[166]

The procedure deals with the analysis of nonconformities identified by quality system processes, initiation of actions to correct and prevent the nonconformities and management review of the actions.

My assessment, based on my experience evaluating these types of documents while at FDA and now in creating them as a consultant, is the documents conform to the requirements of 21 CFR Part 820, FDA recognized standard ISO 14971, and related FDA guidance. They are all consistent with industry practices and standards. The documents I evaluated do not address all the elements of a quality management system, e.g., management controls, CAPA, nonconforming product, etc.

A comprehensive ISO audit or FDA inspection would evaluate the entire quality management system. I am not aware of FDA enforcement action pertaining the ETHICON's quality management system.

Opinion 5. It is my opinion from a regulatory perspective that PROLENE, one of the primary materials used in GYNEMESH PS, is safe and effective; long-term safe and effective performance of PROLENE supports its continued regulatory acceptance as an implantable material.

I believe, based on the regulatory and clinical history of PROLENE containing devices, that FDA and the medical community consider PROLENE containing devices, and therefore PROLENE to be clinically acceptable.

Knitted filaments of extruded PROLENE identical to PROLENE Polypropylene Suture is the primary component in GYNEMESH PS. PROLENE is or was the primary component in many FDA-cleared ETHICON products including, for example, sutures, pelvic mesh, and TVT devices that continue to be marketed like the TVT Classic and the TVT-O.[167] PROLENE is not a new material. PROLENE Polypropylene Suture (Nonabsorbable Surgical Suture USP, Type B) was first regulated by FDA as a drug prior to the enactment of the 1976 medical device amendments to the Federal Food, Drug and Cosmetic Act. FDA approved a New Drug Application (NDA), NDA 16-374, for ETHICON PROLENE Suture (monofilamentous dyed and undyed) over 45 years ago on April 16, 1969.[168] An order approving a new drug is a determination that the drug is safe and effective.[169] The approval for sutures in 1969 made of PROLENE stated the following:[170]

[165] ETH.MESH.05214579-05214621.
[166] ETH.MESH.05444042-05444059.
[167] Comparison of TVT Classic to TVT-O, ETH.MESH.08108658.
[168] ETH.MESH.09625731-09625737. An NDA for a drug is an equivalent submission to a Premarket Approval application for a device.
[169] 21 U.S.C. §355.
[170] ETH.MESH.09625731.

We have completed the review of this application as amended and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved.

The Investigational New Drug application supporting the PROLENE NDA included an assessment of the safety of PROLENE. Studies were conducted evaluating tissue reactions to PROLENE in the rat, rabbit and dog.[171] The full reports were submitted in the NDA as well as other preclinical data.[172] The NDA included extensive clinical data, consisting of numerous investigators and subjects.

The NDA file for the ETHICON PROLENE Suture and subsequent submissions, consisting of supplements, amendments and annual reports, is extensive.[173] Based upon my 37 plus years of experience at FDA and then consulting, I find the PROLENE suture NDA file to be a comprehensive compilation of medical and scientific evidence supporting the safety and effectiveness of PROLENE since it was marketed in 1969. The information submitted to FDA over the years not only meets the NDA requirements it is also consistent with industry standards and best practices for NDA submissions.

The NDA for PROLENE Suture was transferred from the Center for Drug Evaluation and Research to the Center for Devices and Radiological Health. ETHICON continued to comply with NDA/PMA reporting requirements until those NDA/PMA requirements were transformed to 510(k) requirements by the FDA reclassification of nonabsorbable polypropylene surgical sutures from Class III to Class II.[174]

Besides the approved NDA discussed above, FDA had a major opportunity to assess the safety and effectiveness of PROLENE when it classified surgical mesh. When FDA proposed the classification of the preamendments surgical mesh in 1982[175] it considered the recommendations of the General and Plastic Surgery, Orthopedic, and Gastroenterology and Urology Device Panels. In classifying surgical mesh the Panels relied upon their clinical experience with mesh, their review of published clinical data, and their assessment of the risks posed by mesh to health as stipulated in the act regarding classification procedures.[176] FDA finalized the classification of surgical mesh, which includes GYNEMESH PS and TVT devices, into Class II in 1988.[177]

Classification into Class II established that under the law reasonable assurance of safety and effectiveness of surgical mesh would be based upon general controls, including, for example, 510(k) submissions, and any special controls FDA may finalize for the mesh.

I find no evidence in the litigation production, or on FDA's web site of any enforcement action taken by FDA against any PROLENE device or of any recall with a root cause related to the safety or effectiveness of

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[171] ETH.MESH.09626043.
[172] ETH.MESH.09626242-09626359.
[173] Original submission January 17, 1966 supported by IND 1688, 4 original volumes ETH.MESH.00019840-00019846. Subsequent submissions to FDA comprise nearly 50 primary volumes.
[174] ETH.MESH.09634662-09634663.
[175] 47 FR 2810 (January 19, 1982).
[176] 21 USC §360c(b)-(d).
[177] 53 FR 23856 (June 24, 1988).

PROLENE material.[178]

Mr. Gregory R. Jones, Director of Regulatory Affairs when the TVT Classic was first marketed, testified regarding the 510(k) submission of TVT to FDA:[179]

> "PROLENE mesh is well-known, well understood, been on the market for quite some time. PROLENE sutures had been on the market and well-known and well understood. The testing that had been done over the years on PROLENE Suture and PROLENE Mesh was pretty extensive."

The clinical community is supportive of PROLENE as an implantable material. A January 3, 2014, American Urogynecological Society-Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction statement notes the following:[180]

> "Polypropylene material has been used in most surgical specialties (including general surgery, cardiovascular surgery, transplant surgery, ophthalmology, otolaryngology, gynecology, and urology) for over five decades, in millions of patients in the US and the world (personal communication with manufacturers of polypropylene suture and mesh). As an isolated thread, polypropylene is a widely used and durable suture material employed in a broad range of sizes and applications. As a knitted material, polypropylene mesh is the consensus graft material for augmenting hernia repairs in a number of areas in the human body and has significantly and favorably impacted the field of hernia surgery. [6, 7] As a knitted implant for the surgical treatment of SUI, macroporous, monofilament, light weight polypropylene has demonstrated long term durability, safety, and efficacy up to 17 years."

A March 24, 2014, AUGS/SUFU posted additional statements including the following:[181]

> "As an implant for the surgical treatment of SUI, macroporous, monofilament polypropylene has demonstrated long-term durability, safety, and efficacy for up to 17 years [5]."
>
> "Polypropylene is a stable and well-accepted biomaterial with a history of over five decades of use in mesh implants."

The table I constructed in Section III.C. of this report lists numerous 510(k)s for ETHICON mesh devices constructed of PROLENE polypropylene material. Every time FDA cleared one of these mesh devices it reaffirmed the safety and effectiveness of PROLENE. FDA cannot clear a device it considers to be adulterated or misbranded.[182]

FDA maintains knowledge of the performance of devices on the market.

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[178] Recall activities included, for example, instances of counterfeit sutures and delamination reported within limited lots of PROCEED mesh.
[179] Gregory R. Jones deposition, August 20, 2013, Page 185:19-25.
[180] http://sufuorg.com/docs/news/AUGS-SUFU-MUS-Position-Statement-APPROVED-1-3-2014.aspx.
[181] Id.
[182] 21 CFR §807.100(b)(3).

FDA had posted information regarding mesh used for pelvic surgery on the FDA web and it held a public hearing on mesh in 2011 as noted earlier in this report. There were no concerns regarding PROLENE raised at the open public hearing of the FDA advisory committee by any individual. I am not aware of any petition filed with FDA to remove any PROLENE containing devices from the market. FDA continues to clear devices made of PROLENE, such as the TVT Exact in 2013.

It is evident that FDA and the clinical community believe that the benefits of PROLENE outweigh its risks. The FDA and the medical community's pronouncements make it clear that PROLENE is clinically acceptable as an implantable material and products consisting of PROLENE are reasonably safe and effective for their intended use.

Opinion 6. It is my opinion the FDA evaluates safety and effectiveness data for a new device such as GYNEMESH PS in a 510(k).

In August 2010, an FDA 510(k) Working Group carefully assessed the 510(k) program and provided recommendations to senior FDA management.[183] The report states the following in regard to safety and effectiveness determinations in 510(k)s (emphasis added):

> With the exception of certain lower risk devices that are exempt from premarket review, CDRH reviews the safety and effectiveness of medical devices for their intended use prior to marketing. Under the premarket approval (PMA) process, each manufacturer must independently demonstrate reasonable assurance of the safety and effectiveness of its device for its intended use. Under the premarket notification (510(k)) process, CDRH will clear a new device if it finds, through review of a 510(k) submission, that the device is substantially equivalent to a predicate. Generally, predicate devices, as largely class II devices, are those for which there is a reasonable assurance of safety and effectiveness with general and applicable special controls.
>
> The 510(k) program, as it currently exists, is intended to support FDA's public health mission by meeting two important goals: making available to consumers devices that are safe and effective, and fostering innovation in the medical device industry.
>
> When a predicate has a well established risk/benefit profile and is generally well regarded by the healthcare community, a premarket comparison of a new device to that predicate, with sufficient information, can provide reasonable assurance that the device, subject to general and applicable special controls, is safe and effective for its intended use.

[183] CDRH Internal Preliminary Evaluations – Volume 1, 510(k) Working Group, Preliminary Report and Recommendations, http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsand Tobacco/CDRH/CDRHReports/UCM220784.pdf.

The determination of safety and effectiveness in both a PMA and a 510(k) is based on the statutory and regulatory standard of valid scientific evidence, as stated in regulations as follows (emphasis added):[184]

> (1) Although the manufacturer may submit any form of evidence to the Food and Drug Administration in an attempt to substantiate the safety and effectiveness of a device, the agency relies upon only valid scientific evidence to determine whether there is reasonable assurance that the device is safe and effective. After considering the nature of the device and the rules in this section, the Commissioner will determine whether the evidence submitted or otherwise available to the Commissioner is valid scientific evidence for the purpose of determining the safety or effectiveness of a particular device and whether the available evidence, when taken as a whole, is adequate to support a determination that there is reasonable assurance that the device is safe and effective for its conditions of use.
>
> (2) Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. The evidence required may vary according to the characteristics of the device, its conditions of use, the existence and adequacy of warnings and other restrictions, and the extent of experience with its use.

The Act has been amended several times.[185] One such change was the Medical Device User Fee Act of 2002 (MUFMA).[186] According to FDA, MDUFMA was enacted "in order to provide the Food and Drug Administration (FDA) with the resources necessary to better review medical devices, to enact needed regulatory reforms so that medical device manufacturers can bring their safe and effective devices to the American people at an earlier time…"[187]

A guidance issued by FDA on the determination of substantial equivalence notes the following "The 510(k) review standard (substantial equivalence of a new device to a legally marketed

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[184] 21 CFR §860.7(c)(1).
[185] Amendments to the Federal Food, Drug and Cosmetic Act, http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/default.htm.
[186] PL 107-250 (Oct. 26, 2002).
[187] MDUFA, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFMA/ucm109149.htm.

(predicate device) differs from the PMA review standard (reasonable assurance of safety and effectiveness) in that the 510(k) review standard is comparative whereas the PMA standard relies on an independent demonstration of safety and effectiveness. Nonetheless, the principles of safety and effectiveness underlie the substantial equivalence determination in every 510(k) review."[188]

OPINION 7. It is my opinion that the adverse press and litigious environment after the 2011 FDA Safety Notice and the ETHICON decommercialization of transvaginal surgical mesh for pelvic organ prolapse resulted in an atypical surge of MDR reports.

I describe in this report the September 2011 meeting of the FDA Obstetrics and Gynecology Advisory Committee. The Committee discussed the benefits and risks of pelvic mesh and transvaginal tape. On July 13, 2011, FDA posted a Safety Communication of Pelvic Mesh for POP. In this report I describe the change in labeling for GYNEMESH PS to narrow its use to sacroculpopexy procedures.

In my experience, and as I note below from FDA statements and the literature, when a manufacturer removes a medical device from the market, albeit for commercial purposes, those implanted with the device (or who think they may have the device) may become aware of that decommercialization from various sources including, for example, their doctor or from the media, such as lawyer advertisements.[189] Patients with devices no longer on the market may become concerned about the effect, if any, that the device has on their future welfare based on the media reports. Researchers note "Clinicians should be aware of the impact of these advertisements on patient opinion and counsel patients accordingly with unbiased and scientifically accurate information."[190]

During the period from 2011 onward there was considerable public information and media attention on pelvic mesh, including information FDA posted on its web site.[191] Koski's 2014 publication notes the following regarding transvaginal mesh:[192]

[188] Evaluating Substantial Equivalence in Premarket Notifications, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm404770.htm.
[189] Michelle Elaine Koski et al, Patient Perception of Transvaginal Mesh and the Media, Urology 84:575-582.
[190] Id.
[191] Id. and 8/2/15 web search reveals 13,300 results using keywords "pelvic mesh lawsuits."
[192] Id.

> Clinicians have encountered patients with heightened concern regarding the mesh. For example, it is currently not uncommon for patients several years out from a TVM procedure with no complications or symptoms to present questioning whether their mesh should be removed. Although there is a high value in patient awareness of these issues as well as in discussion between patients and physicians, information disseminated in a nonmedical environment and outside of the proper context could result in unnecessary patient anxiety or fear.

FDA believes that effective medical risk communication on matters of public health interest like pelvic mesh is important to inform doctors and assist them with patient care, and to also inform patients and to provide current recommendations and answer questions. At the patient follow up visits the doctor and the patient have the opportunity to discuss this information and the future course of clinical care. The doctor's ability to influence patients' decisions may be hampered when patients become aware of information on a device (that may be biased due to certain pecuniary interests) they may have been treated with before their doctor can inform them of accurate information and discuss it with them.

In its Strategic Plan for Risk Communication[193] FDA states "…the ultimate decision about whether to act on warning information (such as a recall notice) is made by an individual, taking into account the information received, his or her own knowledge, values, and, sometimes, consultation with a medical professional. But each person needs to receive and understand the information necessary to help inform choices.

FDA provides an illustration of challenges with implanted devices as follows:

Example 1: Implanted Devices

The Facts: Many American families have a member with an implanted device helping to keep a regular heartbeat. After years of experience with the device implanted in many people, the manufacturer learns that a small device piece may fail in an extremely small number of people. The manufacturer and FDA decide that devices that have not yet been implanted should be recalled. In most cases, the risks of removing the device outweigh the risks of leaving the device in, given the benefits of the device for the patient. How does communication ensure a successful recall of the remaining devices without causing undue concern for those with the device already implanted?

The Challenge: Some worried patients may make unnecessary office visits, and even potentially harmful decisions about removing a device that is providing a significant benefit—a benefit that outweighs the risk of device failure.

Effective risk communication: Effective risk communication achieves both of the desired ends—an effective recall and an informed patient—in a way that avoids patients making potentially costly and dangerous decisions. This generally means that a complex set of risk and benefit information must be

[193] Strategic Plan for Risk Communication, Urology, 84(3), 2014:575-582. http://www.fda.gov/aboutfda/reportsmanualsforms/reports/ucm183673.htm.

communicated in a way that consumers will attend to, understand, and be able to apply to their individual situations.

In a paper on health care policy and regulatory[194] the authors state "Field actions taken by a manufacturer are often very expensive and come with an attendant amount of attention, publicity, and legal action. While this attention provides significant opportunities to inform physicians and patients, it often leads to fear and—sometimes—inappropriate actions." Physicians and patients may decide to remove devices that are functioning well.

FDA recognized the effect of litigation and other actions on reporting of medical device reports. In information provided to the Orthopedics Advisory Panel in 2012 FDA stated:[195]

> "Recalls, negative media attention, litigation, and increased/decreased usage of a medical device may substantially increase or decrease the number of MDRs received by the FDA. The recall for the DePuy ASR (August 23, 2010) contributed to the sharp increase in MoM THR MDRs received in 2010 and 2011. For example, of the 12,137 MoM THR reports received in 2011, DePuy ASR accounted for 9,006 of these reports (74.2%)."

In my experience in dealing with hundreds of commercial withdrawals of devices or medical device field actions I can confirm the above statement that a commercial withdrawal by a manufacturer followed by the various media concerning the commercial withdrawal result in patient and physician responses that will affect clinical results and may result in increased medical device reports to FDA. In every meeting I had with manufacturers of implants to be withdrawn the risk of unnecessary explants existed and immediate, effective risk communication necessary.

In this report I document the notices sent by ETHICON to physicians about the decommercialization of pelvic mesh.

The following figure displays the atypical surge in GYNEMESH PS and MDRs after the increase in media attention, e.g., lawyer ads, concerning pelvic mesh. The trend of MDR submissions before 2012 was a slowly increasing straight line with 50 reports during 2011. I would have expected during the normal course of reporting that the established trend would continue. However, in 2012 and 2013, after the increase in media attention, the MDR reports increased 10-20 fold.[196] The vast majority of MDR reports during 2012 and 2013 are from attorneys while before 2012 the reports are from the manufacturer or from user facilities.[197]

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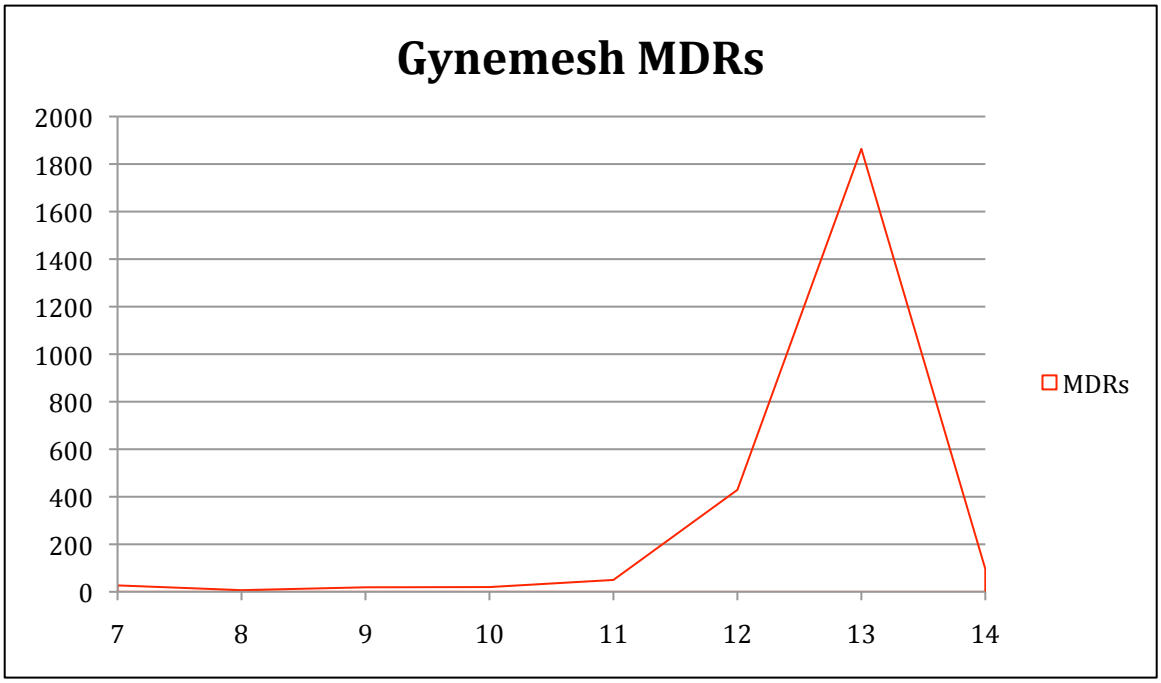
[194] Sharma, A, et. al., Health care policy and regulatory implications on medical device innovations: a cardiac rhythm medical device industry perspective, J Interv Card Electrophysiol. 2013 March; 36(2):107-117.

[195] http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/OrthopaedicandRehabilitationDevicesPanel/UCM309406.pdf.

[196] MDR analysis conducted 2/4/16.

[197] The large uptick in MDRs begins midyear in 2012. The first half of 2012 there were 340 MDRs but the second half there were 883 MDRs.



As I noted, companies and FDA attempt to reduce unnecessary explants through effective risk communication. The FDA has posted on its web site the following information regarding pelvic mesh implants to decrease unnecessary surgeries:[198]

- Continue with your annual and other routine check-ups and follow-up care. There is no need to take additional action if you are satisfied with your surgery and are not having complications or symptoms.

In sum, a surge in MDRs occurred in 2012 and 2013 when media attention, e.g., legal advertisements, increased. This surge skews the probable true clinical risk profiles for the devices. As I note, the unbiased trend is reflected in the pre-2012 MDR submission statistics.

OPINION 8: The Design History File for GYNEMESH PS is substantially compliant with the FDA Quality System regulation.

The FDA Quality System regulation, 21 CFR Part 820, includes the requirement for control of the design of the device to ensure that the specific design requirements are met. The regulation requires the manufacturer to establish and maintain a design history file (DHF) for each type of device. The DHF shall contain or reference the records necessary to demonstrate that the design was developed in accordance with the approved design plan and the requirements of design control.

198 http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/UroGynSurgicalMesh/ucm345205.htm.

I assessed the DHF for GYNEMESH PS/PROLENE Soft.[199] The DHF was produced to me in three files. I evaluated whether the contents of the DHF meet the specific requirements of the design control subsection of the Quality System regulation found in 21 CFR §820.30. The following table lists the requirements and my findings.

DESIGN CONTROL REQUIREMENT	CONTENT OF DHF
Design and development planning	design plans, timelines, quality strategies, clinical/regultory strategies, DDSAs, risk assessment
Design inputs	customer/market requirements
Design outputs	design specifications and output review meetings
Design review	records of periodic meetings with appropriate personnel
Design verification	test reports assessing product charactistics
Design validation	validation protocols and reports
Design transfer	transfer records
Design changes	N/A

My assessment of the contents of the DHF compared to the standard for a DHF (i.e., the Quality System regulation) is that the DHF includes all the information required by the Quality System regulation as I have summarized in the table above. The information and data concerning each aspect of the design and testing of GYNEMESH PS and PROLENE Soft are extensive. The validation reports meet the requirement for a simulated or clinical assessment of the device prior to launch.

OPINION 9: There was ample clinical foundation to support the commercialization of GYNEMESH PS at the time of its launch until ETHICON narrowed the IFU indications for use.

Three separate Clinical Expert Reports (CERs) conducted by ETHICON medical directors assessed the risks and benefits of GYNEMESH PS over the course of its clinical usage. Their assessments included an analysis of the characteristics of GYNEMESH PS, current relevant literature and potential complications.

In his CER dated September 20, 2002, Dr. Martin Weisberg concluded the following:[200]

> The use of GYNEMESH PROLENE Soft Mesh for the purpose of pelvic floor repair i.e. tissue reinforcement and long-lasting stabilization of fascial structures of the pelvic floor in vaginal wall prolapse where surgical treatment is intended either as mechanical support or bridging material for the fascial defect appears to be safe and efficacious on the basis of large scale use of predicate devices over the last decade and a review of the clinical literature as described.

In a second CER dated May 6, 2010, Dr. David Robinson assessed current information on the risks and benefits of GYNEMESH PS, including, for example, current literature and adverse event data, and concluded the

[199] "Books 1-7 2001, ETH.MESH.24910199, 24910558, 24910448, 24911553, 24912026, 24912435, 24912676.
[200] ETH.MESH.03715787-03715793.

following:[201]

> According to the procedures and practices consistent with regulatory guidelines and company policy, the above scores and assessments indicate the need for a complete Risk/Benefit analysis. As a result of this process and a thorough review of all other pertinent information, including: a detailed clinical literature review as provided in Section C of this report and the complaint reviews (internal and MAUDE Database) as provided in Section E, the overall residual risk associated with Gynecare Gynemesh is considered acceptable in view of well documented benefits/patient outcomes.

In a third CER dated April 26, 2013, by Dr. Piet Hinoul, he assessed the risks and benefits of GYNEMESH PS after ETHICON had narrowed the indications for use of GYNEMESH PS to sacrocolpopexy. Dr. Hinoul concludes the following:[202]

> According to the procedures and practices consistent with regulatory guidelines and company policy, the above scores and assessments indicate the need for a complete Risk/Benefit analysis. As a result of this process and a thorough review of all other pertinent information, including: a detailed clinical literature review as provided in Section C of this report and the complaint reviews (internal and MAUDE Database) as provided in Section E, the overall residual risk associated with Gynecare Gynemesh is considered acceptable in view of well documented benefits/patient outcomes.

It is evident to me from a regulatory perspective that the benefits of GYNEMESH PS throughout its period of commercialization have outweighed the risks and therefore the device continued to meet safety and effectiveness standards. FDA permitted GYNEMESH PS to be marketed for over 10 years with implantation transvaginally and abdominally and then continued to allow the device to be implanted only abdominally on the request of ETHICON.

OPINION 10. It is my opinion that a change in material or PROLENE weave specifications for GYNEMESH PS would require the submission of a new 510(k) to FDA and clearance by FDA before the modified device could be marketed.

The composition of the GYNEMESH PS mesh, as described in the original Ethicon 510(k) cleared by FDA is as follows:[203]

> GYNEMESH PROLENE Soft Mesh is the same construction as PROLENE Soft Mesh. GYNEMESH PROLENE Soft Mesh is fabricated from the same knitted monofilaments of natural color and blue pigmented polypropylene, identical in composition to that used in PROLENE Soft Mesh and PROLENE* Polypropylene Sutures.

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[201] ETH.MESH.00082250-00082273.
[202] ETH.MESH.10179518-10179636.
[203] ETH-00823.

Ethicon also stated to FDA that the polypropylene strands used to fabricate PROLENE mesh are the same strands used to fabricate PROLENE polypropylene Nonabsorbable Surgical Suture.[204] Dan Smith, currently an engineering fellow at Ethicon, testified that since the clearance of TVT Classic one clear PROLENE fiber in the mesh construction was replaced with a blue PROLENE fiber.[205] He also testified that there was no standard for mesh pore sizes and the mesh construction is measured or defined in courses and wales per inch, not pore size.

Experts for Plaintiffs proffer opinions that the TVT Classic design and material, which from a materials perspective is relevant to GYNEMESH PS, presented safety and effectiveness concerns and Ethicon should have considered alternative materials and designs.[206] For example, Dr. Klinge has stated:

> There are alternative design characteristics that would be safer in a woman's pelvic tissues as a treatment for incontinence than some of the design characteristics of the Prolene mesh in TVT. One such safer alternative design would be a mesh product with less material and larger distance between the mesh fibers (Ethicon's Ultrapro mesh has 3-5mm between the fibers and has a weight of 25 g/m2).
>
> Another safer design would be a polymer that elicits a more favorable inflammatory response. PVDF, as a synthetic, non-absorbable suture or mesh material has improved textile and biological properties over polypropylene. It is thermally stable and more abrasion resistant than other flouroplastics and induces a minimal cellular response, shows exceptional chemical stability and has excellent resistance to aging. PVDF sutures are routinely used in cardiovascular and orthopaedic surgery.[178]

And Dr. Elliot has discussed the characteristics of TVT and a "Prolene Mesh Improvement Project." Dr. Iakovlev has discussed an alternative material called PVDF.

The experts for Plaintiffs do not state whether any of the changes they proffer would be subject to FDA clearance of a new 510(k). The fact is that a new material or significant specifications changes to PROLENE described by Plaintiffs experts would have required a new 510(k).

I assessed the proffered changes as I did for 25 years as a premarket submission evaluator using FDA regulations and related guidance as a basis for my assessment. The FDA regulation for 510(k) submissions, 21 CFR Part 807, requires a new 510(k) be submitted for a marketed device as follows:[207]

> (3) The device is one that the person currently has in commercial distribution or is reintroducing into commercial distribution, but that is about to be significantly changed or modified in design, components, method of manufacture, or intended use. The following constitute significant changes or modifications that require a premarket notification:

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[204] ETH.MESH.08476244.
[205] Smith deposition, 2/3/14, Pages 721:19-24 and 727:22-25.
[206] Expert Reports 8/24/15, Prof. Dr. Med. Uwe Klinge, Bruce Rosenzweig, MD, Jerry G. Blaivas, MD, Dr. Daniel Elliot, Dr. Vladimir Iakovlev.
[207] 21 CFR §807.81(a)(3).

> (i) A change or modification in the device that could significantly affect the safety or effectiveness of the device, e.g., a significant change or modification in design, material, chemical composition, energy source, or manufacturing process. (ii) A major change or modification in the intended use of the device.

FDA guidance provides direction to the industry on the types of changes to an existing device cleared under a 510(k) that may be significant.[208] The guidance states the following:

> **Will the material of the affected part of the implant be likely to contact body tissues or fluids?** Changes in materials that contact body tissues or fluids may critically affect the device's safety or effectiveness, either because of potentially new interactions of the device material on the body or because of the body's environmental effects on the new material in the device. Manufacturers should submit a new 510(k) for a change in implant material where the material contacts tissue (including bone tissue) or body fluid.

In addition to the above recommendation by FDA the decision flowcharts in the guidance make it clear that a material change or formulation change, e.g., a weave change, to an implanted device leads to a new 510(k). In addition, Ethicon would be required to verify and validate the changes to the GYNEMESH PS as required by the quality system regulation.

Some changes to the GYNEMESH PS PROLENE material would not require a new 510(k). Each change should be preceded by an assessment by Ethicon of the regulatory impact of the change. A change in color of the PROLENE strands, laser cutting or minor changes in the manufacturing process such as those listed in a deposition testimony exhibit[209] would not require a new 510(k) but would require consideration by Ethicon of the need for verifications and revalidation per the quality system regulation.

I reserve the right to amend my opinions pending further discovery and to address any relevant expert reports for Plaintiffs.

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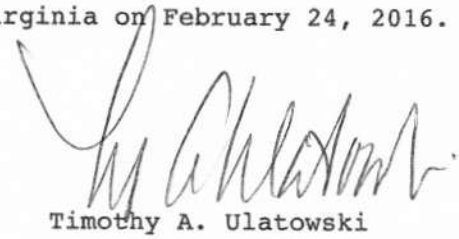
[208] Deciding When to Submit a 510(k) for a Change to an Existing Device (K97-1), http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080235.htm.

[209] ETH.MESH.10633520.

Executed in Herndon, Virginia on February 24, 2016.



Timothy A. Ulatowski

GYN PS

APPENDIX A: CV

Timothy A. Ulatowski

[redacted]

Consultant, Medical Devices

Extensive Regulatory Experience ~ Risk Management ~ Technical Expert

A unique medical device consultant with extensive experience in both premarket evaluation of new medical devices and enforcement of FDA laws and regulations. Over 36 years of significant public health achievements, creating major regulatory programs and policies, developing and implementing strategic and risk management plans, and building collaborations with global regulatory partners and industry. Proven skills in advising industry on regulatory issues, assessing compliance and enforcement actions, evaluating premarket documents, managing and supervising large organizations, resolving complex technical and scientific problems of individual firms to those of national and international scope, and communicating to diverse audiences.

Selection of Notable Accomplishments

Hands on technical leadership of numerous compliance, enforcement and recall actions, many of national and global importance

Initiated use of novel corporate enforcement actions

Created effective internal quality management system used as a model program in FDA

Lead author of international guidance documents on aspects of the Global Harmonization Task Force medical device regulatory model

Recognized in “Top 100” of medical device professionals/MDDI

Primary reviewer of hundreds of Premarket Notifications, Investigational Device Exemptions, Premarket Approval Applications, recalls and compliance actions

Leader of team that developed the current FDA device standards program

Author of many key FDA premarket guidance documents, technical standards and publications

FDA key witness in federal court (US v Abtox), contributor to many court cases, advisor to DOJ and FDA criminal investigations office

Lead for agency on many GAO, OMB and Congressional activities

FDA spokesperson to major press and to large audiences

HHS Team Leader and technical expert remediating Anthrax contamination of Senate and Postal Service buildings

Creator of FDA/CDC/EPA tripartite collaborations on chemical germicides and co-author of current FDA/EPA national regulatory scheme for chemical germicides

Co-author and collaborator on sharps injury prevention guidance, related OSHA and NIOSH regulations and policies, resulting in documented reduction of injuries

Recipient of numerous major FDA awards

Professional Experience

Independent Consultant

May 2014 - present

Becker & Associates Consulting Inc./NSF Health Sciences: Expert Consultant then employee

September 2011 – April 2014

- Provided effective and timely solutions to a variety of medical device regulatory issues
- Created and evaluated premarket submissions, quality systems, compliance, and device reporting
- Provided Training on FDA medical device requirements
- Expert witness

NDA Partners LLC: Principal

January 2011 – June 2012

- Advised clients on FDA regulations and law regarding product submissions, compliance and enforcement actions, and postmarket surveillance activities
- Served as an expert witness in litigation
- Conducted due diligence

FDA, CDRH: Director, Office of Compliance and Senior Advisor for Enforcement

January 2003 – January 2011

- Managed and supervised office of four divisions and 180 professional staff responsible for ensuring compliance with medical device laws and regulations
- Directed FDA device quality system and bioresearch enforcement programs
- Directed inspection assignments and assessed quality system and bioresearch monitoring inspection reports and company/investigator/sponsor/IRB responses to determine violations
- Worked with all FDA districts, ORA and drug, biologics and food compliance executives to formulate enforcement strategies and actions
- Hands on evaluation and management of recalls, device advertising and promotion, MDRs, registration and listing, and medical device field resource allocation and prioritization
- Created new device enforcement policies and programs, directed implementation of the Commissioner's strategic action items, and participated in executive strategic planning at the agency and center levels
- Co-leader of FDA Medical Device Field Committee, an ORA/CDRH collaboration
- Initiated comprehensive training program for compliance staff and web-based information for the public

- Co-leader of 2010 user fee legislation post market committee, devising proposals and strategies with key Center and Agency staff for next round of legislation
- Senior Device Enforcement Advisor September 2010 – January 2011

FDA, CDRH: Head of USA Delegation, Global Harmonization Task Force and FDA representative to GHTF Study Group 1 Premarket

January 1995 - October 2010

- Managed the activities of the USA FDA participants to the GHTF Steering Committee and the five study groups; collaborated with USA industry task force members, USA leader on the GHTF Steering Committee for last four years
- Coordinated creation and review of documents and recommended agency decisions on pending documents to Center Director
- Primary author of several GHTF documents, including the original premarket "STED" document, and Global Model document, which are now used internationally
- Frequently trained international government staff on GHTF and FDA procedures

FDA, CDRH/Office of Device Evaluation: Director, Division of Dental, Anesthesiology, General Hospital, and Infection Control Devices

December 1996 – January 2003

- Managed premarket activities, such as review of premarket submissions and investigational applications, panel meetings, guidance development, and collaborative support for other CDRH offices
- Led development of the division during a major reorganization
- FDA lead on numerous international standards committees, reengineering task groups, and interagency task forces dealing with significant public health issues
- Succeeded in reducing review times while improving the quality and rigor of reviews
- Primary reviewer on numerous 510(k)s, IDEs, and PMAs
- Agency and ISO technical expert on medical device sterilization and disinfection

Prior to 1996 FDA and other experience, short summary

Device Evaluation Associate Director, Branch Chief and front line 510(k), IDE, and PMA reviewer

Director, Investigational Device Staff, IDE application review and protocol advice

New Drug Evaluation Product Manager, NDA and IND activities and advisory committee exec sec

Microbiologist, National Center for Antibiotic Analysis, drug assessments

Prior to college and FDA career: US Army 1968 – 1971

Education

- Master of Science/Physiology with Biomedical Engineering emphasis, 1988 GPA 4.0

Georgetown University School of Medicine

- Bachelor of Science/Microbiology, 1974 cum laude

Pennsylvania State University

APPENDIX B: Materials Reviewed and Public Sources of References

FDA web site
Federal Register
Federal Food, Drug and Cosmetic Act
Code of Federal Regulations

Additional references provided by Butler Snow

Appendix C: Prior Testimony

Depositions:

University of Pittsburgh of the Commonwealth System of Higher Education d/b/a University of Pittsburgh v. Varian Medical Systems, Inc.

Civil Action No.: 2:08-cv-01307 (USDC, Western District of Pennsylvania)

David M. Kloss, et al, v. I-Flow Corporation, et al, Case No. 2:10-cv-00295-JFC (USDC, Western District of Pennsylvania)

Retractable Technologies, Inc. and Thomas Shaw v. Becton, Dickinson and Company, Civil Action No.2:08-cv-16 (Folsom) (USDC, Eastern District of Texas Marshall Division)

Diagnostic Devices Inc, v. Pharma Supply, Inc. et al, Diagnostic Devices Inc, v. Taidoc Technology Corporation, Case No.3:08-CV-00149-MOC-DCK (USDC, Western District of North Carolina, Charlotte Division)

Brenda F. Kitrosser v. Nuvasive, Inc. et al., Case No: 37-2009-00099700-CU-MM-CTL [Consolidated with Case No: 37-2010-00099400-CU-PO-CTL] (Superior Court of the State of California In and For the County of San Diego, Central Branch)

Superior Court of New Jersey, Law Division, Atlantic County

In re Pelvic Mesh/ Gynecare Litigation, Case No.291 CT, Master Case 6341-10

Jackson, et al v DePuy Orthopedics, No. CAL 10-32147 (Prince George's County, MD)

Strum v. DePuy Orthopaedics, Inc., et al., No. 11 L 009352 (Circuit Court, Cook County, Illinois)

Dorney-Madgitz v. DePuy Orthopedics, Inc., et al., 5:11-cv-001240-RBS (USDC, Eastern District of Pennsylvania)

Weinstat, et al. v. Dentsply International, et al., San Francisco Superior Court No. CGC-04-432370

Braun v. Medtronic Sofamor Danek, USDC, District of Utah, Central Division, Case 2:10-cv-01283

Connie Schubert and Kevin Schubert v. Ethicon, Inc., Ethicon Women's Health and Urology, a division of Ethicon, Inc., Gynecare, and Johnson and Johnson, et. al., In the Circuit Court of Jasper County, Missouri at Joplin, Case No. 10AO-CC00219

Sekisui America Corporation and Sekisui Medical Co., Ltd. v. Richard Hart and Mary Louise Trudel-Hart, USDC, Southern District of New York, Case 1:12-cv-03479-SAS (for Plaintiff)

Carol Lewis and Kenneth Lewis v. Ethicon, USDC, Southern District of West Virginia, MDL No. 2327

April Christine Cabana v. Medtronic Inc. (et al), Superior Court of the State of California, County of Los Angeles, Case No. BC 465 313

Christine Napolitano v. Synthes, Inc., USDC, District of Connecticut, Civil Action 3:09-CV-00828

Herlihy-Paoli v. DePuy Orthopedics, Inc., et al, 3:12-CV-04975-K (USDC, Northern District of Texas, Dallas Division)

City of Lakeland Employees Pension Plan v. Baxter International Inc., No. 10-cv-6016, USDC, Northern District of Illinois

Smith v. Baxano, Inc. et al, Superior Court of Washington for Snohomish County, Case No. 13-2-02714-1

Andrea Smith v DePuy Orthopedics, et al., District Court of Tulsa County, Oklahoma, No. CJ-2011-05804

Zimmer NexGen Knee Implant Products Liability Litigation, USDC, Northern District of Illinois, Eastern Division, MDL No. 2272, Master Docket No.:1:11-cv-05468

Sandra Garcia v Rodolfo J. Walss, MD, Johnson & Johnson, Inc. and Ethicon, Inc., District Court, 103rd Judicial District, Cameron County, Texas, Cause No. 2013-DCL-3511-D

Laura Ness v Depuy Orthopedics, Inc., et al., In the Circuit Court for Baltimore City, Case No. : 24-C-14-002465

Consolidated Fresenius Cases, Commonwealth of Massachusetts, Middlesex SS., Superior Court Department of the Trial Court, Civil Action No. 2013-03400-O Session

Aoki, Christopher, Greer, Klusmann, Peterson, Thibodeau (separate Plaintiffs) v DePuy Orthopedics, Inc. et al,. USDC, Northern District of Texas, Dallas Division, MDL No. 2244

Center City Periodontists, P.C., et al. v. Dentsply International, Inc., Eastern District of Pennsylvania, Civil Action No. 10-00744.

Michael Parker, Individually and Amy Parker, Individually v. Veronica A. Vasicke, MD; Bluegrass Orthopedics & Hand Care, PSC; and I-Flow Corporation, Fayette Circuit Court, Eighth Division, Civil Action No. 12-CI-3543.

Court Testimony:

Strum v. DePuy Orthopaedics, Inc., et al., No. 11 L 009352 (Circuit Court, Cook County, Illinois)

Brenda F. Kitrosser v. Nuvasive, Inc. et al., Case No: 37-2009-00099700-CU-MM-CTL [Consolidated with Case No: 37-2010-00099400-CU-PO-CTL] (Superior Court of the State of California In and For the County of San Diego, Central Branch)

Weinstat, et al. v. Dentsply International, et al., San Francisco Superior Court No. CGC-04-432370

Sekisui America Corporation and Sekisui Medical Co., Ltd. v. Richard Hart and Mary Louise Trudel-Hart, USDC, Southern District of New York, Case 1:12-cv-03479-SAS

Becky S. Anderson v. Medtronic, Inc. (et al), Superior Court for the State of Washington, County of King, No. 12-2-17928-0 SEA

Donald Gustafson v. Zimmer, Inc., District Court, Collin County, Texas, 366th Judicial District, Cause No. 366-03111-2011

Herlihy-Paoli v. DePuy Orthopedics, Inc., et al, 3:12-CV-04975-K (USDC, Northern District of Texas, Dallas Division)

Andrea Smith v DePuy Orthopedics, et al., District Court of Tulsa County, Oklahoma, No. CJ-2011-05804

Alysia Ogburn-Sisneros, as personal representative of the estate of Billy Ogburn, Sr., Plaintiff v. Fresenius Medical Care Holdings, Inc.d/b/a Fresenius Medical Care North America, Inc, Fresenius USA, Inc., Fresenius USA Manufacturing, Inc., Fresnius USA Marketing, Inc., and Fresenius USA Sales, Inc., Defendants, Commonwealth of Massachusetts, Superior Court Department, Civil Action No. 13-5050

Center City Periodontists, P.C., et al. v. Dentsply International, Inc., Eastern District of Pennsylvania, Civil Action No. 10-00744.

ATTACHMENTS

SUBMISSIONS REFERENCES ON PAGES 38, 43-44 WITHOUT BATES NUMBERS

2007/2008 PROFESSIONAL SLIDE DECK WITHOUT BATES NUMBERS

August 3,2012 letter to Dr. med. Kurt Lobodasch